Synthesis of a 2,3-Di-*O*-substituted Heptose Structure by Regioselective 3-*O*-Silylation of a 2-*O*-Substituted Heptose Derivative

Kazuyuki Ishii,[a] Yasuaki Esumi,[b] Youhei Iwasaki,[a] and Ryohei Yamasaki*[a]

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A 3,4-diol derivative of 2-*O*-benzyl (Bn) heptose (Hep), methyl 6,7-di-*O*-acetyl-2-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (**3**), was treated with both triethylsilyl (TES) and *tert*-butyldimethylsilyl (TBDMS) chlorides to regioselectively form the 3-*O*-silyl ethers **4** and **6**, respectively. To examine whether silylation of the 3,4-diol of a 2-*O*-substituted disaccharide also gives the corresponding 3-*O*-silylated disaccharide, we synthesized α-$GlcN_3$-(1→2)-Hep **11a** by coupling a Hep 2-OH acceptor **9** with a $GlcN_3$ trichloroacetimidate **10**. As expected from the results obtained using the 2-*O*-Bn Hep **3**, treatment of α-$GlcN_3$-(1→2)-Hep-3,4-diol **14** with TESCl followed by acetylation gave only the 3-*O*-TES **15**. Compound **14** was converted into the 3-OH acceptor **16** by silylation/acetylation — without isolating **15** — and subsequent acid hydrolysis. By coupling the disaccharide 3-OH acceptor **16** with per-*O*-benzylated β-lactosyl trichloroacetimidate **17**, we obtained the desired 2,3-branched tetrasaccharide, α-Lac-(1→3)-[α-$GlcN_3$-(1→2)]-Hep **18a**. Hydrogenation of **18a**, followed by *N*-acetylation, gave α-Lac-(1→3)-[α-GlcNAc-(1→2)]-Hep **22**. Thus, we synthesized the 2,3-dibranched Hep by utilizing the 2-*O*-substituted Hep. This regioselective *O*-3-silylation of the 2-*O*-substituted Hep provides an intermediate that can be utilized for the synthesis of not only 2,3- and 3,4-dibranched Hep but also the 2,3,4-tribranched Hep structures present in lipooligo- and lipopolysaccharides produced by pathogenic Gram-negative bacteria.

Introduction

Pathogenic Gram-negative bacteria such as the Neisserial and Haemophilus species produce glycolipid antigens called lipooligosaccharides (LOS).[1] LOS, which consist of the oligosaccharide[2−6] (OS) moiety and the lipid A, are considered as vaccine targets against those pathogenic bacteria.[7−11] A carbohydrate epitope within LOS produced by a strain of *Neisseria gonorrhoeae* 15253[8,9,11,12] is one of those targets, and we have been focusing our efforts in constructing the OS of 15253 LOS.[11,13,14]

The OS of 15253 LOS[12] contains two dibranched heptose (Hep) residues: 3,4- and 2,3-dibranched Hep. The synthesis of the former structure is described in the preceding paper;[15] this paper describes the construction of the latter. The 2,3-dibranched Hep expressed in 15253 LOS is a tetrasaccharide, and *N*-acetyl-D-glucosamine (GlcNAc) and lactose (Lac) are α(1→2)- and α(1→3)-linked to Hep, respectively. The 2,3-dibranched structure is expressed in not only Haemophilus LOS[16,17] but also in Campylobacter LOS.[1] Therefore, it is important to establish a synthetic methodology for obtaining this branched structure.

In a recent paper, we described the synthesis of α-lactosyl-(1→3)-Hep by glycosidating methyl 2-*O*-Bn-4,6-*O*-benzylidene-7,8-dideoxy-*manno*-oct-7-enopyranoside with a per-*O*-benzylated β-lactosyl trichloroacetimidate to obtain the α-lactosylated product as a reference compound.[14] The resulting trisaccharide cannot, however, be directly utilized for the synthesis of the 2,3-dibranched structure because selective removal of the benzyl protecting group of *O*-2 cannot be accomplished under hydrogenolysis conditions without affecting the per-*O*-benzylated lactose residue at *O*-3. To utilize a 2-*O*-Bn Hep derivative, which is readily available from its mannose counterpart,[13] as a starting material for the synthesis of the branched Hep structures, we examined the selective protection of the 3-OH group of the 2-*O*-substituted Hep containing unprotected hydroxy groups at both the *C*-3 and *C*-4 positions. We found that treating the 3-OH group of the 2-*O*-Bn-Hep-3,4-diol with silyl chlorides gave the corresponding 3-*O*-silylated products in high yields. Similarly, silylation of a 3,4-diol derivative of α-$GlcN_3$-(1→2)-Hep gave only the 3-*O*-silylated product. By using this selective 3-*O*-silylation of the 3,4-diol, we synthesized the desired 2,3-dibranched structure expressed in 15253 LOS.[12]

[a] Department of Biochemistry & Biotechnology, Tottori University,
Koyama-Minami 4-101, Tottori City,
Tottori-Ken 680-8553, Japan
Fax: (internat.) + 81-857-31-5347
E-mail: yamasaki@muses.tottori-u.ac.jp
[b] The Institute of Physical and Chemical Research (RIKEN)
Wako-shi,
Saitama 351-0198, Japan

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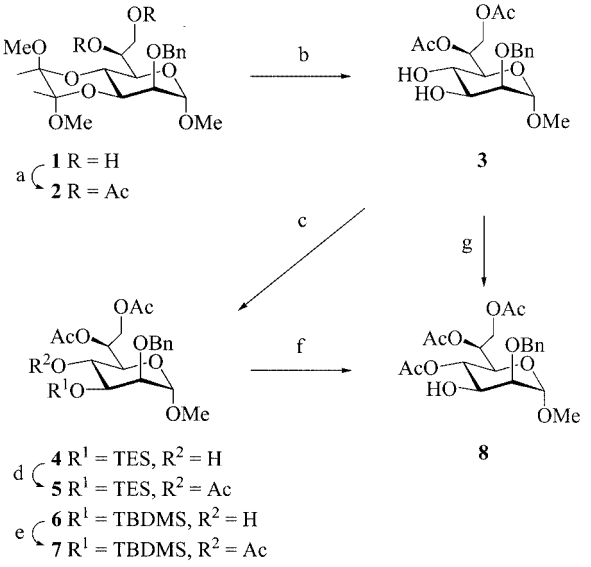
Results and Discussion

The reactivity of the secondary hydroxy groups within methyl α-D-mannoside towards silyl chlorides decreases in the order 2-OH > 3-OH >> 4-OH, i.e., the 4-OH group is the least active of the three.[18−21] The inactivity of the 4-OH group of the mannoside prompted us to utilize a 2-*O*-substituted *manno*-heptopyranoside to accomplish regioselective silylation of the 3-OH group. To examine the reactivity of the 3-OH group against TESCl and TBDMSCl, we used methyl 6,7-di-*O*-acetyl-2-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (**3**) as a substrate (Scheme 1).



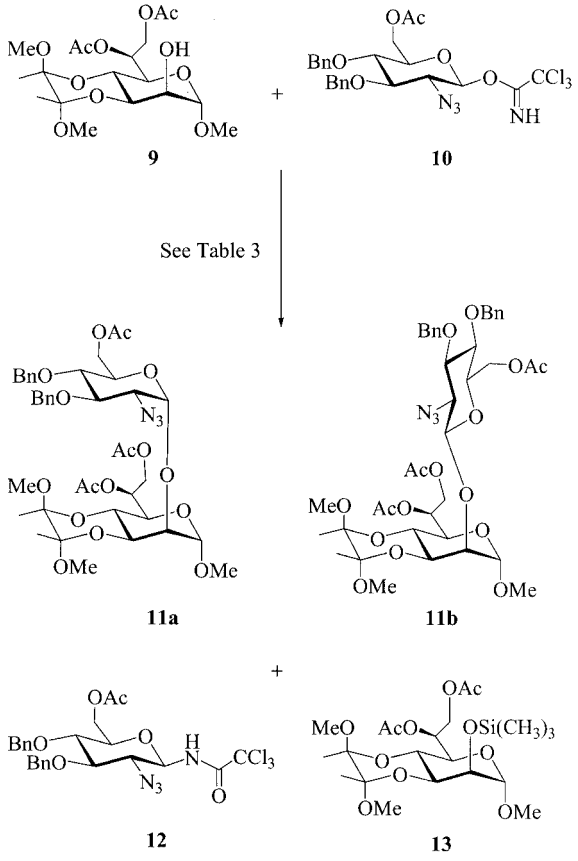
Scheme 1. a) Ac_2O, DMAP, pyridine, quantitative; b) TFA/water (9:1, v/v), 91%; c) TESCl, pyridine, 0 °C, 90% or TBDMSCl, imidazole, DMF, 94%; d) Ac_2O, pyridine, 93%; e) Ac_2O, DMAP, pyridine, 97%; f) 1% (w/v) I_2 in MeOH for **5**, 88%; TFA/water (9:1, v/v) for **7**, 93%; g) 1. TESCl, pyridine; 2. Ac_2O, pyridine; 3. TFA/water (9:1, v/v), 91%

This 3,4-diol **3** was prepared in 91% yield by acetylation of (3′*S*,4′*S*)-methyl 2-*O*-benzyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-*glycero*-α-D-*manno*-heptopyranoside (**1**)[13] in acetic anhydride (Ac_2O)/pyridine and subsequent hydrolysis of **2** in trifluoroacetic acid (TFA)/water (Scheme 1). Treatment of the 3,4-diol **3** with 2.2 molar equiv. of TESCl in pyridine at 0 °C for 10 min, followed by chromatographic purification, gave only the 3-*O*-TES ether **4** in 90% yield. Similarly, the 3-*O*-TBDMS ether **6** was obtained in 94% yield by treating **3** with 2 molar equiv. of TBDMSCl and imidazole in *N*,*N*-dimethylformamide (DMF) for 4.5 h at room temperature. The locations of the silyl groups of **4** and **6** were also confirmed by NMR spectroscopy of their corresponding 4-*O*-acetates **5** and **7** that were obtained upon acetylation with Ac_2O/pyridine; the signals of the H-4 protons of both **4** and **6** were deshielded after acetylation (Table 1), which confirmed that the 3-OH group was silylated.

The 3-*O*-TES ether of compound **5** was removed by treating it with 1% iodine (w/v) in methanol (MeOH)[22] at room temperature to give the 3-OH product **8** in 88% yield. Although de-*O*-silylation of the 3-*O*-TBDMS ether **7** did not reach completion when using either I_2/MeOH or tetrabutylammonium fluoride (TBAF) buffered with acetic acid (AcOH),[23] the TBDMS group was removed by treating **7** for 15 min in TFA/water (9:1, v/v)[24] to give **8** in 93% yield. Compound **8** was also prepared from **3** in 91% yield by sequentially carrying out the silylation, acetylation, and subsequent hydrolysis steps without isolating **4** and **5**. Thus, we confirmed that silylation of the 3,4-diol of 2-*O*-Bn-Hep **3** proceeded regioselectively to give the 3-*O*-silylated compound in high yields. We then examined whether a 3,4-diol of α-$GlcN_3$-(1→2)-Hep could be silylated regioselectively to give the 3-*O*-protected product, a useful intermediate for the synthesis of the 2,3-di-*O*-substituted Hep structure present in 15253 LOS.[12]

Prior to silylation, we examined glycosylation conditions for the synthesis of α-$GlcN_3$-(1→2)-Hep by coupling a Hep acceptor **9** with 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl trichloroacetimidate (**10**)[25] (Scheme 2).

The acceptor **9** was obtained in 97% yield after hydrogenolysis of **2** over 10% Pd/C, and its structure was con-



Scheme 2

Table 1. ^{1}H NMR (500 MHz) data recorded in $CDCl_3$ at 25 °C for compounds **2**−**9**, **11a**, **11b**, and **14**−**16**

Compound[a]	Residue	H-1 ($^3J_{1,2}$)	H-2 ($^3J_{2,3}$)	H-3 ($^3J_{3,4}$)	H-4 ($^3J_{4,5}$)	H-5 ($^3J_{5,6a}$)	H-6a ($^3J_{5,6b}$)	H-6b ($^2J_{6a,6b}$)	H-7a ($^3J_{6,7a}$)	H-7b ($^3J_{6,7b}$)	($^2J_{7a,7b}$)
2		4.75	3.69	4.70	4.19	3.92	5.45	−	4.24	4.31	
		(1.0)	(2.8)	(10.5)	(10.0)	(2.0)	−	−	(6.5)	(6.5)	(11.0)
3		4.81	3.75	3.84	3.55	3.67	5.44	−	4.31	4.38	
		(1.5)	(3.0)	(9.5)	(9.5)	(1.5)	−	−	(5.5)	(7.5)	(11.0)
4		4.73	3.60	3.93	3.70	3.65	5.49	−	4.31	4.35	
		(1.5)	(3.0)	(9.0)	(10.0)	(1.5)	−	−	(5.5)	(7.5)	(10.0)
5		4.73	3.64	4.07	5.43	3.84	5.21	−	4.21	4.34	
		(1.5)	(2.5)	(10.0)	(10.0)	(2.0)	−	−	(5.5)	(7.5)	(11.0)
6		4.73	3.61	3.94	3.69	3.65	5.48	−	4.31	4.35	
		(1.5)	(3.0)	(9.0)	(10.0)	(1.5)	−	−	(6.0)	(7.0)	(11.0)
7		4.74	3.64	4.05	5.45	3.86	5.21	−	4.21	4.34	
		(1.5)	(2.5)	(9.5)	(10.0)	(2.5)	−	−	(7.5)	(5.5)	(11.0)
8		4.82	3.74	3.84	5.09	3.89	5.32	−	4.25	4.34	
		(1.5)	(3.5)	(10.0)	(10.0)	(2.0)	−	−	(5.5)	(8.0)	(11.5)
9		4.79	3.92	4.01	4.06	3.95	5.44	−	4.24	4.32	
		(1.0)	(3.0)	(10.3)	(10.0)	(1.5)	−	−	(7.0)	(6.5)	(11.0)
11a	Hep	4.77	3.97	4.08	4.30	3.92	5.46	−	4.23	4.31	
		(1.5)	(3.0)	(10.0)	(10.3)	(1.5)	−	−	(6.5)	(6.5)	(12.0)
	$GlcN_3$	5.41	3.23	4.12	3.55	3.95	4.24	4.31			
		(4.0)	(10.5)	(9.0)	(10.3)	(5.0)	(2.0)	(12.0)			
11b	Hep	4.87	4.02	4.07	4.13	3.92	5.44	−	4.24	4.32	
		(1.0)	(2.5)	(10.0)	(10.0)	(1.5)	−	−	(7.0)	(6.5)	(11.0)
	$GlcN_3$	4.50	3.55	3.42	3.59	3.40	4.22	4.42			
		(8.5)	(9.3)	(9.5)	(9.5)	(3.5)	(2.5)	(12.0)			
14	Hep	4.80	3.86	3.87	3.53	3.66	5.43	−	4.30	4.32	
		(< 1.0)	n.d.	(9.5)	(9.8)	(1.5)	−	−	(6.0)	(7.5)	(11.5)
	$GlcN_3$	5.06	3.49	3.88	3.54	4.05	4.22	4.31			
		(3.5)	(10.3)	(9.0)	(10.0)	(4.5)	(2.5)	(12.3)			
15	Hep	4.81	3.83	4.11	5.46	3.82	5.13	−	4.18	4.33	
		(1.0)	(3.0)	(10.0)	(10.5)	n.d.	−	−	(7.5)	(6.0)	(11.0)
	$GlcN_3$	5.02	3.28	4.09	3.55	4.08	4.30−4.24				
		(3.5)	(10.0)	(9.0)	(10.0)	n.d.	n.d.	n.d.			
16	Hep	4.85	3.85	3.92	5.13	3.88	5.27	−	4.24	4.32	
		(1.5)	(3.0)	(10.0)	(10.0)	(2.0)	−	−	(8.0)	(5.5)	(11.0)
	$GlcN_3$	5.02	3.56	3.99	3.56	4.15	4.24	4.32			
		(4.0)	(10.0)	(9.5)	(10.3)	(5.0)	(2.5)	(12.0)			

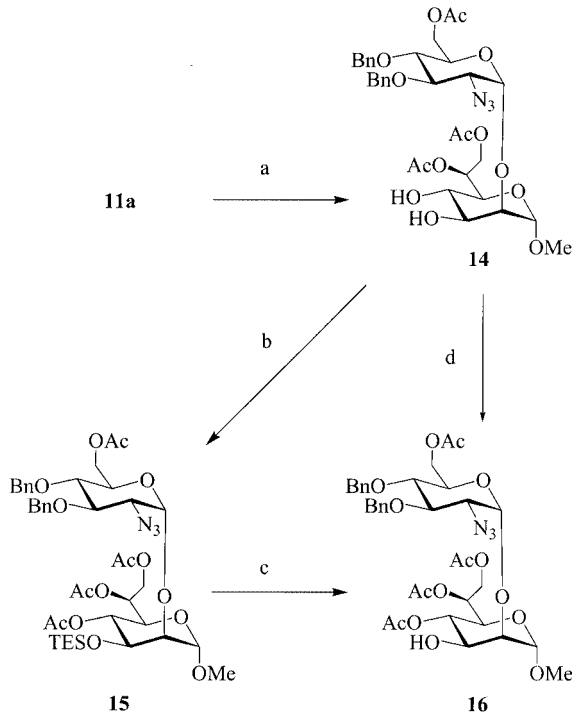
[a] The ^{1}H NMR spectroscopic chemical shifts (ppm) were determined by analyzing 2D NMR spectroscopic data (DQF-COSY, HMQC and HMBC) comparatively, and the *J* couplings (Hz) were obtained by analyzing either the DQF-COSY or 1D NMR spectra. The ^{1}H NMR spectroscopic chemical shifts of other protons are listed in the Exp. Sect. n.d.: not determined.

firmed by the downfield and upfield shifts of the signals of the H-2 proton (Table 1) and the C-2 carbon (Table 2), respectively, that occurred upon removal of the benzyl protecting group. Table 3 summarizes the results of glycosylation of the acceptor **9** with 1.6 molar equiv. of the donor **10** in either 1,4-dioxane[14,26,27] or Et_2O[27−29] when using trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a promoter; the isolated yields of the (1→2)-linked disaccharides **11a** and **11b** were in the range 29−80%. The acceptor **9** was first treated with **10** in 1,4-dioxane using 0.04 molar equiv. of TMSOTf, i.e., conditions used previously for 3-*O*-α-lactosylation of a *manno*-oct-7-enopyranoside derivative.[14] The combined yield, however, of the glycosides **11a** and **11b** was only 29%, and the β-*N*-glycoside **12** (16%) was also obtained (Entry 1). The use of 0.2 molar equiv. of TMSOTf increased the yield slightly (Entry 2), and, in addition to **12**, the 2-*O*-trimethylsilyl (TMS) derivative **13** was formed, which explains the lower recovery of the unreacted acceptor **9**. In contrast, glycosylations in Et_2O (Entries 3 and 4) gave much better yields of **11a** and **11b** (77−80%) than those in 1,4-dioxane, although the *N*-glycoside **12** and the 2-*O*-TMS ether **13** were also isolated; the best yield (80%) was obtained with the reaction using 0.04 molar equiv. of TMSOTf (Entry 3). The ratio, however, of **11a** and **11b** in Et_2O was ca. 3:1, and the glycosylations in this solvent were not stereospecific when compared with the results that had been reported previously.[27−29] The conditions for α-selective glycosylation in the synthesis of **11a** could be optimized by utilizing a glycosyl fluoride or thioglycoside as a donor or by examining whether the use of a donor carrying an electron-withdrawing substituent at *O*-3 would affect the outcome of the stereospecificity of the reaction, as has been observed with glycosylation using a $GlcN_3$ trichloroacetimidate derivative.[30]

Table 2. ^{13}C NMR (125 MHz) data recorded in $CDCl_3$ at 25 °C for compounds **2**−**9**, **11a**, **11b**, and **14**−**16**

Compound[a]	Residue	C-1	C-2	C-3	C-4	C-5	C-6	C-7
2		100.5	75.2	69.0	62.6	68.7	67.6	61.7
3		98.8	77.2	70.8	67.5	70.6	73.0	62.6
4		99.9	78.0	73.3	62.7	71.1	69.2	62.7
5		100.2	78.1	71.2	67.8	69.0	67.3	62.3
6		100.0	77.4	72.8	67.0	71.2	69.2	62.7
7		100.3	78.0	71.3	67.7	69.0	67.3	62.3
8		100.2	78.1	71.2	67.8	69.0	67.3	62.3
9		101.3	69.5	68.3	62.1	68.2	67.5	61.6
11a	Hep	100.2	73.0	68.6	62.3	68.7	67.1	61.6
	$GlcN_3$	98.3	63.3	79.1	79.1	69.4	62.8	
11b	Hep	99.4	74.7	67.6	62.2	68.8	67.4	61.6
	$GlcN_3$	100.0	66.2	83.2	76.8	73.1	62.5	
14	Hep	99.7	79.2	70.8	67.7	70.4	69.1	62.5
	$GlcN_3$	99.5	64.1	80.7	77.9	69.8	62.7	
15	Hep	99.3	78.1	70.1	67.5	68.9	67.2	62.1
	$GlcN_3$	99.9	63.5	79.5	77.9	69.5	62.9	
16	Hep	99.5	80.4	69.9	67.9	68.2	67.2	62.7
	$GlcN_3$	99.7	64.3	81.0	77.8	70.0	62.2	

[a] The ^{13}C NMR spectroscopic chemical shifts (ppm) were determined by analyzing 2D NMR spectroscopic data (DQF-COSY, HMQC and HMBC) comparatively. Only the data for the skeletal carbon atoms are presented, and those for other carbon atoms are listed in the Exp. Sect.



Scheme 3. a) TFA/water (9:1, v/v), 95%; b) 1. TESCl, pyridine, 0 °C → room temp.; 2. Ac_2O, pyridine, 88%; c) TFA/water (9:1, v/v), 99%; d) 1. TESCl, pyridine, 0 °C → room temp.; 2. Ac_2O, pyridine; 3. TFA/water (9:1, v/v), 88%

The structure of each disaccharide of **11a** and **11b** was confirmed by 2D NMR spectroscopy in a similar manner to that described previously[11,13−15] (Tables 1 and 2). The anomeric configurations of the disaccharides were identified by the $^3J_{1,2}$ values (4.0 and 8.5 Hz for the α- and β-anomers, respectively) and the value of the ^{13}C-1 chemical shift of each $GlcN_3$ residue. The downfield ^{13}C-2 shift of each Hep residue of **11a** and **11b** (Table 2), and the HMBC experiment, also confirmed the $GlcN_3$ linkage site.

The α-$GlcN_3$-(1→2)-Hep derivative **11a** was hydrolyzed in TFA/water (9:1) to remove the butane-2,3-diacetal (BDA) unit to give the 3,4-diol **14** (95%), which was used for silylation (Scheme 3).

As expected from the results of silylation of **3**, treatment of **14** with 3 molar equiv. of TESCl in pyridine, followed by acetylation with Ac_2O/pyridine, gave the 3-*O*-TES ether **15** in 88% yield. The signal of the Hep H-4 proton of **15** was shifted downfield ($\Delta\delta$ = 1.93 ppm) relative to that of **14**, which confirmed the location of the silyl group (Table 1). The results of silylation of **14**, taken together with those of **3**, demonstrate that the 3-OH group of the 2-*O*-substituted Hep 3,4-diol is highly reactive toward silylation reagents when compared with the 4-OH group, as predicted from the results of silylation of methyl α-D-mannoside;[18−21] the reaction proceeded regioselectively to yield the 3-*O*-silylated product in high yields. Regeneration of the 3-OH group was accomplished by hydrolyzing **15** in 9:1 TFA/water at room temperature, and the α-$GlcN_3$-(1→2)-Hep derivative bearing a free 3-OH group (**16**) was obtained in 99% yield. Compound **16** was obtained in 88% yield from **14** by sequentially carrying out the silylation/acetylation and subsequent hydrolysis without isolating **15**. Thus, we obtained the 3-OH acceptor **16** that is suitable for the construction of the 2,3-di-*O*-substituted Hep structure present in 15253 LOS.[12]

The 3-OH acceptor **16** was coupled with 1.9−2.5 molar equiv. of a donor, per-*O*-benzylated lactosyl trichloroacetimidate **17**,[14] at room temperature in 1,4-dioxane or Et_2O

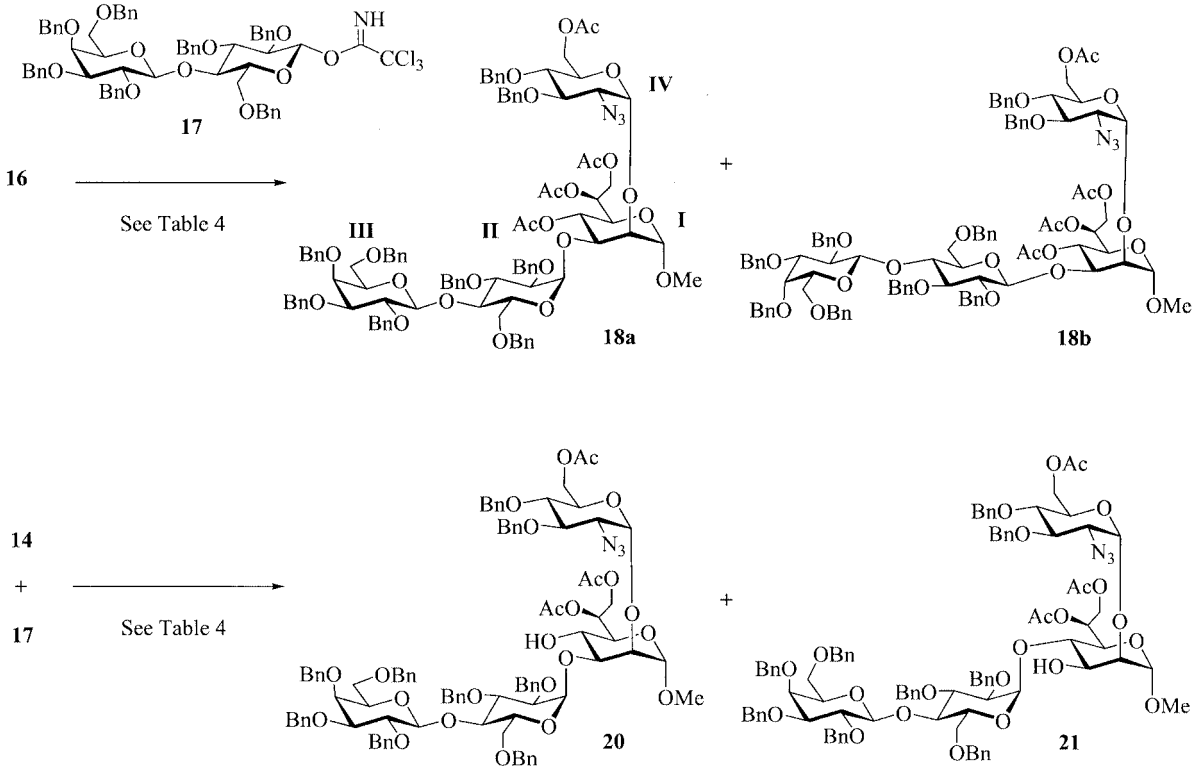
Table 3. Glycosylation of the acceptor **9** with the donor **10** (the acceptor **9** was treated with 1.6 molar equiv. of the donor **10** at room temp.)

Entry	TMSOTf (equiv.)[a]	Solvent	Isolated yields (%) α-(1→2) **11a**[b]	β-(1→2) **11b**[b]	Recovered **9**[b]	*N*-glycoside **12**[c]	2-*O*-TMS **13**[b]	Ratio **11a**:**11b**
1	0.04	dioxane	23	6	63	16	–	3.8:1
2	0.2	dioxane	26	7	48	5	14	3.7:1
3	0.04	Et_2O	58	22	11	8	–	2.6:1
4	0.2	Et_2O	56	21	4	9	14	2.7:1

[a] The amounts of TMSOTf are based on the quantity of the donor. [b] The yields are expressed in reference to the quantity of the acceptor **9**. [c] The yields are expressed in reference to the quantity of the donor **10**.

using TMSOTf as a promoter (Scheme 4); the results are summarized in Table 4. Glycosylation using 0.04 molar equiv. of TMSOTf in 1,4-dioxane (Entry 1 of Table 4), conditions employed in a previous study,[14] gave the expected 3-*O*-lactosylated products **18a** and **18b** in only 30% yield. In contrast to the glycosylations using **9** as an acceptor, the use of 0.2 molar equiv. of TMSOTf in 1,4-dioxane (Entry 2) improved the yield (64%), and the β-*N*-glycosylated product **19** was also obtained. When Et_2O was used as the solvent (Entries 3 and 4), the tetrasaccharides **18a** and **18b** were obtained in 84−85% yields even though they were purified by gel permeation chromatography (Sephadex LH-20) and subsequent flash column chromatography, and the best yield (77%) of the desired α-glycoside **18a** was obtained when 0.04 molar equiv. of TMSOTf was used. These results confirmed again that Et_2O is a better solvent than 1,4-dioxane in the case of these glycosylations. Also, as Table 4 (Entries 1−4) shows, the glycosylations in both solvents gave much better α-selectivity (α/β, 7−9:1) than those of **9** with **10** (Table 3).

In addition to **16**, we used the 3,4-diol **14** as an acceptor, expecting that formation of 3-*O*-substituted tetrasaccharide would be a dominant reaction pathway based on the results of both the silylation described above and the glycosylation of a tetra-*O*-acetyl mannosyl trichloroacetimidate with 4,6-*O*-benzylidene mannoside reported in the preceding paper.[15] The yield, however, of the α-(1→4) tetrasaccharide **21** exceeded that of the desired α-(1→3) tetrasaccharide



Scheme 4

Table 4. Glycosylation of the acceptors **14** and **16** with the donor **17** (reactions were carried out at room temp.)

Entry	Acceptor	TMSOTf (equiv.)[a]	Solvent	Isolated yield (%) α-Linked tetrasaccharides[b]	β-Linked tetrasaccharide[b]	Recovered **16** or **14**[b]	*N*-Glycoside **19**[c]	Ratio α:β
1[d]	**16**	0.04	dioxane	27	3	67	n.d.[e]	9.0:1
2[f]	**16**	0.2	dioxane	58	6	28	13	9.7:1
3[f]	**16**	0.04	Et_2O	77	8	10	32	9.6:1
4[f]	**16**	0.2	Et_2O	74	10	7	n.d.[e]	7.4:1
5[g]	**14**	0.04	dioxane	52[h]	16[i]	21	n.d.[e]	3.3:1

[a] The amounts of TMSOTf are based on the quantity of the donor **17**. [b] The yields are expressed in reference to the quantity of the acceptor **16**. [c] The yields are expressed in reference to the quantity of the donor **17**. [d] Treated with 1.9 molar equiv. of the donor **17**. [e] n.d. = not determined. [f] Treated with 2.5 molar equiv. of the donor **17**. [g] Treated with 1.7 molar equiv. of the donor **17**. [h] α-(1→3)-Linked **20** and α-(1→4)-linked tetrasaccharide **21** were isolated in 24 and 28% yields, respectively. [i] A mixture of tetrasaccharides, presumably β-(1→3)- and β-(1→4)-linked.

Table 5. ^{1}H NMR (500 MHz) data recorded in $CDCl_3$ at 25 °C for compounds **18a**, **18b**, and **20**−**23**

Compound[a]	Residue	H-1 ($^3J_{1,2}$)	H-2 ($^3J_{2,3}$)	H-3 ($^3J_{3,4}$)	H-4 ($^3J_{4,5}$)	H-5 ($^3J_{5,6a}$)	H-6a ($^3J_{5,6b}$)	H-6b ($^2J_{6a,6b}$)	H-7a ($^3J_{6,7a}$)	H-7b ($^3J_{6,7a}$)	($^2J_{7a,7b}$)
18a	Hep	4.82	4.11	4.02	5.51	3.84	5.09	−	4.16	4.31	
		(< 1.0)	(2.5)	(10.0)	(10.0)	(2.0)	−	−	(7.5)	(6.0)	(10.5)
	$GlcN_3$	5.02	3.00	4.10	3.41	4.19	4.15	4.28			
		(3.5)	(10.0)	(9.5)	(9.5)	n.d.	n.d.	n.d.			
	Glc	4.89	3.40	3.97	3.69	4.26	3.72	3.75			
		(4.0)	(9.5)	(9.5)	(9.5)	(6.0)	n.d.	(10.3)			
	Gal	4.30	3.82	3.40	3.87	3.35	3.28	3.40			
		(8.0)	(9.8)	(3.0)	n.d.	n.d.	n.d.	n.d.			
18b	Hep	4.80	4.03	4.19	5.49	3.88	5.24	−	4.18	4.32	
		(< 1.0)	n.d.	(9.5)	(10.0)	(2.0)	−	−	(7.0)	(5.5)	(11.0)
	$GlcN_3$	5.12	2.66	3.94	3.32	3.97	4.18	4.25			
		(3.5)	(10.3)	(9.5)	(9.8)	(5.0)	(2.0)	(12.0)			
	Glc	4.50	3.37	3.57	3.93	3.39	3.74−3.80				
		(7.5)	(8.5)	(9.5)	(9.5)	n.d.	n.d.	n.d.			
	Gal	4.43	3.75	3.40	3.90	3.32	3.30	3.46			
		(7.5)	(9.5)	(3.5)	n.d.	n.d.	n.d.	n.d.			
20	Hep	4.78	3.92	3.81	3.96	3.70	5.47	−	4.23	4.31	
		(1.5)	(3.0)	(9.5)	(9.5)	(1.5)	−	−	(7.5)	(6.0)	(11.0)
	$GlcN_3$	4.93	2.94	3.99	3.39	4.09	4.15	4.26			
		(3.5)	(10.0)	(9.5)	(10.0)	(5.0)	(2.0)	(12.0)			
	Glc	4.93	3.48	4.02	3.81	4.13	3.68	3.80			
		(3.5)	(9.8)	(9.5)	(10.0)	(1.5)	(5.0)	(10.3)			
	Gal	4.31	3.80	3.38	3.89	3.37	3.36	3.47			
		(8.0)	(10.3)	(2.5)	n.d.	(5.0)	(10.0)	(11.5)			
21	Hep	4.74	3.98	3.79	4.05	3.79	5.18	−	4.25−4.30		
		(1.0)	n.d.	(10.0)	(10.0)	n.d.	−	−	n.d.	n.d.	n.d.
	$GlcN_3$	5.31	3.25	4.08	3.54	4.05	4.25	4.30			
		(4.0)	(10.5)	(9.5)	(8.5)	n.d.	(2.5)	(12.0)			
	Glc	5.04	3.49	3.87	4.03	4.07	3.79	3.98			
		(4.0)	(10.0)	(9.5)	(9.8)	n.d.	n.d.	n.d.			
	Gal	4.33	3.72	3.28	3.85	3.31	3.39	3.49			
		(7.5)	(10.0)	(3.0)	n.d.	(5.0)	(7.5)	(9.5)			
22	Hep	4.86	3.96	4.24	5.48	3.85	5.15	−	4.16	4.31	
		(1.5)	(4.0)	(10.0)	(10.0)	(1.5)	−	−	(6.5)	(5.5)	(11.0)
	GlcNAc	4.86	4.43	3.80	3.62	4.17	4.19	4.24			
		(3.5)	(9.5)	(9.5)	(9.5)	n.d.	n.d.	n.d.			
	Glc	4.92	3.48	3.27	3.79	3.75	3.56	3.72			
		(3.0)	(9.5)	(9.0)	(9.3)	(5.0)	n.d.	(10.5)			
	Gal	4.26	3.75	3.35	3.86	3.30	3.23	3.39			
		(7.5)	(9.8)	(2.5)	n.d.	(5.0)	(8.0)	(9.0)			
23	Hep	4.90	3.95	4.05	5.50	3.86	5.24	−	4.20	4.33	
		(< 1.0)	n.d.	(10.0)	(10.0)	(1.5)	−	−	(7.5)	(5.5)	(11.5)
	GlcNAc	5.13	4.46	5.30	5.15	4.25	4.09	4.25			
		(3.5)	(10.0)	(10.0)	(9.5)	n.d.	n.d.	n.d.			
	Glc	5.10	4.79	5.24	3.64	3.84	4.12	4.33			
		(3.5)	(10.3)	(9.8)	(10.0)	(6.5)	n.d.	(11.5)			
	Gal	4.47	5.06	4.95	5.34	3.87	4.04	4.12			
		(8.0)	(10.8)	(4.0)	(1.0)	(7.5)	(6.5)	(11.5)			

[a] The ^{1}H NMR spectroscopic chemical shifts (ppm) were determined by analyzing 2D NMR spectroscopic data (DQF-COSY, HMQC and HMBC) comparatively, and the *J* couplings (Hz) were obtained by analyzing either the DQF-COSY or 1D spectra. The ^{1}H NMR spectroscopic chemical shifts of other protons are listed in the Exp. Sect.; n.d.: not determined.

20, and a mixture of tetrasaccharides, presumably the β-(1→3) and β-(1→4)-linked products, was also obtained (Table 4, Entry 5). Since glycosylation using the 3,4-diol **14** as an acceptor was not regioselective, we did not explore any further glycosylation conditions using **14** for the synthesis of the 2,3-dibranched structure.

The structures of the tetrasaccharides **18a**, **18b**, **20**, and **21** were determined by 2D NMR spectroscopy in a similar manner to that described earlier. Although the introduction of the perbenzylated lactose unit made the spectral assignment rather difficult, the ^{1}H and ^{13}C NMR spectroscopic chemical shifts of each tetrasaccharide were determined by analyzing the corresponding DQF-COSY, HMQC, and HMBC NMR spectra comparatively and also by examining the previous data[14] for the 3-*O*-lactosylated Hep (Tables 5 and 6). As an example, parts of the HMQC (panels A and B) and HMBC (panels C and D) NMR spectra of **18a** are presented in Figure 1. The existence of the (1→3) linkage

Table 6. ^{13}C NMR (125 MHz) data recorded in $CDCl_3$ at 25 °C for compounds **18a**, **18b**, and **20**−**23**

Compound[a]	Residue	C-1	C-2	C-3	C-4	C-5	C-6	C-7
18a	Hep	99.5	78.2	77.7	65.6	68.9	67.2	62.0
	$GlcN_3$	100.2	63.0	79.5	79.0	69.5	63.0	
	Glc	99.5	78.3	79.9	78.3	71.4	69.2	
	Gal	103.6	79.7	82.8	73.5	73.3	68.3	
18b	Hep	99.8	73.4	74.7	65.1	69.1	67.1	62.2
	$GlcN_3$	98.3	62.8	79.7	77.7	69.4	62.9	
	Glc	100.1	81.1	83.3	76.7	75.1	68.2	
	Gal	102.8	79.9	82.5	73.5	73.0	67.9	
20	Hep	99.8	78.9	81.2	65.6	70.5	68.3	62.4
	$GlcN_3$	100.0	62.8	79.3	78.3	69.4	63.0	
	Glc	101.0	78.7	80.4	77.4	71.4	68.5	
	Gal	103.3	79.8	82.5	73.7	73.3	68.3	
21	Hep	99.9	76.4	71.8	78.9	68.4	68.7	61.4
	$GlcN_3$	99.3	63.2	79.4	78.3	69.3	62.9	
	Glc	101.0	78.5	80.3	76.0	71.4	67.1	
	Gal	102.6	79.9	82.4	73.9	73.2	68.3	
22	Hep	99.3	77.9	74.9	66.0	69.0	67.0	62.1
	GlcNAc	98.0	52.7	81.7	77.4	70.0	63.0	
	Glc	99.9	78.7	80.1	77.6	71.6	68.3	
	Gal	103.5	79.7	82.6	73.4	73.1	68.2	
23	Hep	99.3	77.2	75.6	65.4	69.1	66.7	62.0
	GlcNAc	96.2	51.6	70.8	68.2	68.4	62.2	
	Glc	99.0	70.9	69.2	76.4	69.4	62.1	
	Gal	101.2	68.8	71.1	66.6	70.5	60.7	

[a] The ^{13}C NMR spectroscopic chemical shifts (ppm) were determined by analyzing 2D NMR spectroscopic data (DQF-COSY, HMQC and HMBC) comparatively. Only the data for the skeletal carbon atoms are presented, and those for other carbon atoms are listed in the Exp. Sect.

peaks, Glc H-1/Hep C-3 and Hep H-3/Glc C-1; other cross-relay peaks labeled in the panels C and D also confirmed the structure of **18a**. The $^3J_{1,2}$ value of the Glc residue (Table 5) verified its anomeric configuration.

Finally, we investigated reaction conditions for the conversion of the azide (N_3) unit of the tetrasaccharide **18a** into an acetamide (NHAc) group (Table 7). Reductive *N*-acetylation of **18a** using thioacetic acid (AcSH)/pyridine[31] was very sluggish: the acetamide **22** was obtained in 68% yield after treatment of the mixture at 40 °C for 12 days. Therefore, we examined two other methods to perform this conversion: treatment with zinc powder/AcOH[32] or hydrogenation over Lindlar catalyst[33] followed by *N*-acetylation. Reduction with Zn was also slow (8 days at room temperature) and subsequent *N*-acetylation gave **22** in the same yield as the reaction with AcSH/pyridine (Scheme 5). A sequence, however, of hydrogenation of **18a** over Lindlar catalyst, *N*-acetylation, and subsequent chromatographic purification gave the desired compound **22** in 89% yield.[33] Thus, we successfully constructed the 2,3-di-*O*-substituted Hep structure, α-Lac-(1→3)-[α-GlcNAc-(1→2)]-Hep **22**.

As described earlier, we accomplished selective 3-*O*-silylation of the Hep 3,4-diol and then regenerated the 3-OH acceptor for the synthesis of the 2,3-dibranched Hep structure. Selective protection of the Hep 3-OH group has been achieved by selective *O*-alkylation of a 2,3-diol using either a phase-transfer method[34,35] or a tin intermediate.[10,34,35] The drawback of the *O*-alkylation method is that the reac-

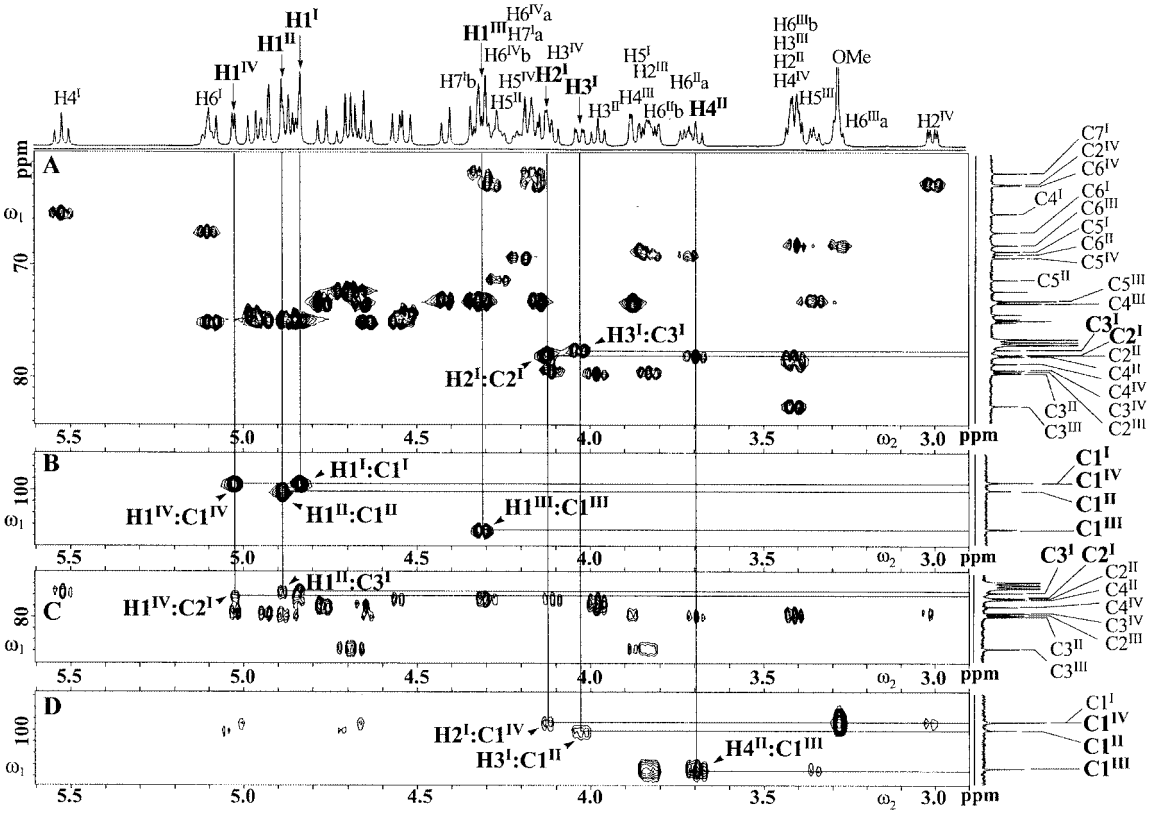
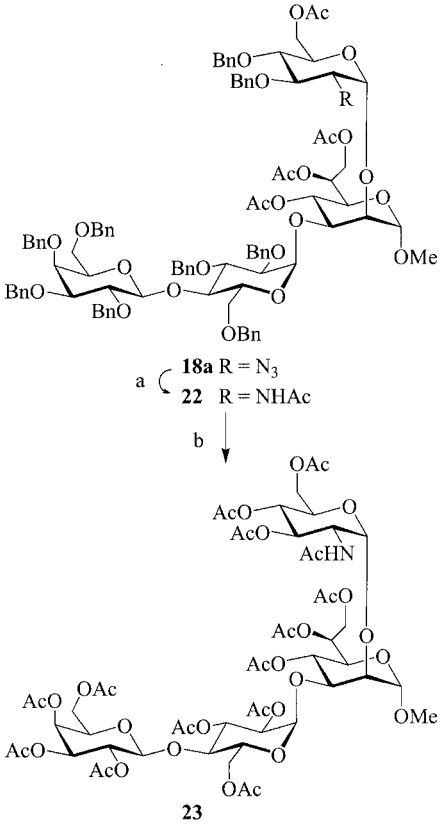


Figure 1. Partial HMQC (panels A and B) and HMBC (panels C and D) spectra of compound **18a** in $CDCl_3$ at 25 °C; only partial $^{13}C/^1H$ cross-peaks (A and B) and cross-relay peaks (C and D) are labeled; both ^1H (ω_2) and ^{13}C (ω_1) signals due to the CH_2-Ph unit are not labeled; each Roman numeral in panels A−D corresponds to that of **18a** as shown in Scheme 4

Table 7. Conversion of azide **18a** into acetamide **22**

Experimental conditions	Yield (%)
Lindlar cat./H_2 followed by *N*-acetylation	89
AcSH/pyridine at 40 °C for 12 days	68
Zn/AcOH followed by *N*-acetylation	68



Scheme 5. a) See Table 7; b) 1. H_2, Pd/C, MeOH/EtOH/AcOH (2:1:0.1, v/v/v); 2. Ac_2O, pyridine, 98%

tion is not highly regioselective and tends to give the 3-*O*-alkyl ether in only moderate yields. Alternatively, the 3-OH acceptor has been prepared by esterification of a 2,3-orthoester and subsequent treatment with aqueous TFA.[36,37] The yield of chloroacetylation[37] of the 2,3-orthoester, however, is not as high as that of acetylation,[36] which is a situation that may be a drawback for the synthesis of the 3,4-di-*O*-substituted Hep. In addition, the 2,3-orthoester intermediate may not be utilized directly for the synthesis of the 2,3-dibranched Hep structure. In contrast, both regioselective *O*-3-silylation and regeneration of the 3-OH group were accomplished in high yields, and the 3-*O*-silyl ethers **4** and **6** can be employed directly for the synthesis of the 3,4-di-*O*-substituted Hep. In addition, by using an appropriate silyl ether that is stable under the conditions of hydrogenolysis, the 2,3,4-tri-*O*-substituted Hep expressed in Neisserial[38] and Campylobacter LOS[39] can be synthesized from the 3-*O*-silyl intermediate. Therefore, in terms of the ease and yields of protection and deprotection, and the versatility of the 3-*O*-silyl ether intermediate for the synthesis of branched Hep structures, regioselective 3-*O*-silylation of the 2-*O*-substituted Hep has advantages over the existing procedures[34−37] described above. Although we did not examine silylation of a 2-*O*-substituted mannoside in the present study, its regioselective 3-*O*-silylation could possibly be accomplished in a similar manner; such *O*-3 silylation would be useful also for the manipulation of the secondary hydroxy groups of mannose.

Conclusions

In summary, we have found that the 3,4-diol derivatives of both 2-*O*-Bn Hep and α-GlcN_3-(1→2)-Hep can be silylated regioselectively to give the corresponding 3-*O*-protected products in high yields. By coupling the 3-OH acceptor generated from the 3-*O*-silylated α-GlcN_3-(1→2)-Hep with the per-*O*-benzylated lactosyl trichloroacetimidate, we synthesized the 2,3-dibranched Hep structure, α-Lac-(1→3)-[α-GlcN_3-(1→2)]-Hep, in high yield and converted its azide unit to an acetamide group by hydrogenation and subsequent *N*-acetylation. Thus, we constructed the 2,3-branched Hep, α-Lac-(1→3)-[α-GlcNAc-(1→2)]-Hep, that is present in 15253 LOS.[12] The 3-*O*-silyl derivative of the 2-*O*-substituted Hep is a useful intermediate for preparing the 2,3-dibranched compound and could also be utilized for the synthesis of both 3,4-dibranched and 2,3,4-tribranched structures.

Experimental Section

General: Optical rotations and melting points (uncorrected) were measured using a HORIBA SEPA-200 polarimeter and a YANAGIMOTO micro melting point apparatus, respectively. Elemental analyses were performed using a Vario El III apparatus (Elementar Analysensysteme GmbH., Germany). High-resolution fast-atom bombardment mass spectrometry (HR-FABMS) was performed as described previously.[14] High-resolution electrospray-ionization mass spectrometry (HR-ESIMS) was carried out in the positive-ion mode using a JEOL JMS-T100LC spectrometer with methanol as the mobile phase at a flow rate of 0.2 mL/min (internal standard: sodium trifluoroacetate); samples were dissolved in methanol at a concentration of ca. 1 μg/mL and 10 μL was injected. All NMR spectra were recorded at 25 °C in $CDCl_3$ using a JEOL JNM-ECP 500 MHz NMR spectrometer equipped with a Silicon Graphics O_2 computer. Chemical shifts are reported in ppm relative to internal tetramethylsilane (δ_H = 0.00 ppm) for ^{1}H NMR and $CDCl_3$ (δ_C = 77.00 ppm) for ^{13}C NMR spectra. 2D NMR spectroscopic data (DQF-COSY, HMQC, and HMBC) were processed using a Delta program (JEOL USA. Inc.) in a similar manner described previously.[13,14] Silica gel 60 (E. Merck) was used for flash column (0.040−0.063 mm) and open column (0.063−0.200 mm) chromatography. Silica gel 60 F_{254} (E. Merck) was used for thin-layer chromatography (TLC), and compounds were detected under UV light or by spraying with 10% conc. sulfuric acid in methanol and then heating the plates at 120 °C for 5 min. Glycosylation reactions were carried out at room temp. under argon atmospheres using dry solvents. The reaction mixtures were filtered through Celite and the filtrates were washed with water, dried with $MgSO_4$, and concen-

trated to a syrup in vacuo under 40 °C unless otherwise stated. The following compounds were prepared according to literature procedures: (3′*S*,4′*S*)-methyl 2-*O*-benzyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-*glycero*-α-D-*manno*-heptopyranoside (**1**),[13] 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranosyl trichloroacetimidate [**10**; m.p. 105−106 °C (recrystallized from Et_2O/hexane), $[\alpha]_D^{26} = +4.0$ (c = 1.5, $CHCl_3$) {ref.[25] (as a syrup) $[\alpha]_D^{24} = +6.8$ (c = 1.5, $CHCl_3$)}], and 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl trichloroacetimidate (**17**).[14]

(2′*S*,3′*S*)-Methyl 6,7-Di-*O*-acetyl-2-*O*-benzyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-*glycero*-α-D-*manno*-heptopyranoside (2): Compound **1**[13] (3.00 g, 7.00 mmol) was treated with Ac_2O/pyridine (1:2, v/v, 30 mL) containing a catalytic amount of 4-dimethylaminopyridine (DMAP) at room temp. for 12 h. The mixture was concentrated to a syrup that was purified by open column chromatography (hexane/EtOAc, 2:1) to give the title compound **2** (3.59 g, ca.100%) as a syrup. $[\alpha]_D^{25} = +130$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 1.28, 1.33 (s, 3 H each, BDA-CH_3), 2.04 (s, 3 H, COCH_3), 2.09 (s, 3 H, COCH_3), 3.17 (s, 3 H, OCH_3), 3.27, 3.29 (s, 3 H each, BDA-OCH_3), 4.69, 4.92 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.25−7.44 (m, 5 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 17.81 (BDA-CH_3), 17.84 (BDA-CH_3), 20.8 (COCH_3), 20.9 (COCH_3), 47.8 (BDA-OCH_3), 48.0 (BDA-OCH_3), 54.7 (OCH_3), 72.9 (CH_2-Ph), 99.8 (BDA-C_q), 100.0 (BDA-C_q), 127.4, 128.0 (2 C), 128.1 (2 C), 138.6 (aromatic *C*), 170.4 ($COCH_3$), 170.5 ($COCH_3$) ppm. HR-ESIMS: calcd. for $C_{25}H_{36}O_{11}Na$ $[M + Na]^+$: 535.2155; found 535.2133.

Methyl 6,7-Di-*O*-acetyl-2-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (3): Compound **2** (3.60 g, 7.02 mmol) was treated with TFA/water (9:1, v/v, 30 mL) at room temp. for 20 min. The reaction mixture was concentrated to a syrup using toluene as an azeotrope, and purification by open column chromatography (hexane/EtOAc, 1:2 → 1:3 → 1:4) gave the title compound **3** (2.54 g, 91%) as a syrup. $[\alpha]_D^{25} = -10$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 2.07 (s, 3 H, COCH_3), 2.17 (s, 3 H, COCH_3), 2.46 (br. s, 1 H, 3-O*H*), 3.17 (br. s, 1 H, 4-O*H*), 3.34 (s, 3 H, OCH_3), 4.62, 4.74 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.26−7.35 (m, 5 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 20.7 (COCH_3), 20.9, (COCH_3), 55.1 (OCH_3), 73.0 (CH_2-Ph), 127.7 (2 C), 127.9, 128.5 (2 C), 137.72 (aromatic C), 170.5 ($COCH_3$), 172.0 ($COCH_3$) ppm. HR-ESIMS: calcd. for $C_{19}H_{26}O_9Na$ $[M + Na]^+$: 421.1475; found 421.1480.

Methyl 6,7-Di-*O*-acetyl-2-*O*-benzyl-3-*O*-triethylsilyl-L-*glycero*-α-D-*manno*-heptopyranoside (4): TESCl (347 μL, 2.06 mmol) was added slowly to a solution of compound **3** (412 mg, 1.03 mmol) in pyridine (3 mL) at 0 °C and then the reaction mixture was stirred for 10 min at 0 °C. The reaction mixture was poured into ice-water and extracted with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (hexane/EtOAc, 2:1) gave the title compound **4** (482 mg, 90%) as an oil. $[\alpha]_D^{24} = -40$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 0.63−0.68 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.95−0.98 [m, 9 H, Si(CH$_2$CH_3)$_3$], 2.05 (s, 3 H, COCH_3), 2.14 (s, 3 H, COCH_3), 2.72 (d, $^3J_{4\text{-OH,H-4}}$ = 3.5 Hz, 1 H, 4-O*H*), 3.31 (s, 3 H, OCH_3), 4.68, 4.79 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.25−7.37 (m, 5 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 4.9 [Si(CH_2CH$_3$)$_3$], 6.9 [Si(CH$_2$$CH_3$)$_3$], 20.8 (CO$CH_3$), 20.9 (CO$CH_3$), 55.0 (O$CH_3$), 72.5 ($CH_2$-Ph), 127.5, 127.7 (2 C), 128.2 (2 C), 138.4 (aromatic *C*), 170.5 ($COCH_3$), 171.7 ($COCH_3$) ppm. $C_{25}H_{40}O_9Si$ (512.67): calcd. C 58.57, H 7.86; found C 58.31, H 7.64.

Methyl 4,6,7-Tri-*O*-acetyl-2-*O*-benzyl-3-*O*-triethylsilyl-L-*glycero*-α-D-*manno*-heptopyranoside (5): A solution of compound **4** (157 mg, 0.306 mmol) in Ac_2O/pyridine (1:2, v/v, 6 mL) was stirred for 19 h at room temp. The mixture was concentrated to a residue that was purified by flash column chromatography (hexane/EtOAc, 2:1) to give the title compound **5** (166 mg, 97%) as a pale-yellow oil. $[\alpha]_D^{24} = +5$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 0.54−0.65 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.93−0.96 [m, 9 H, Si(CH$_2$CH_3)$_3$], 2.04 (s, 3 H, COCH_3), 2.05 (s, 3 H, COCH_3), 2.10 (s, 3 H, COCH_3), 3.32 (s, 3 H, OCH_3), 4.68, 4.91 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.25−7.41 (m, 5 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 4.9 [Si(CH_2CH$_3$)$_3$], 6.8 [Si(CH$_2$$CH_3$)$_3$], 20.75 (CO$CH_3$), 20.83 (CO$CH_3$), 21.1 (CO$CH_3$), 55.1 (O$CH_3$), 73.6 ($CH_2$-Ph), 127.5, 127.7 (2 C), 128.2 (2 C), 138.5 (aromatic *C*), 169.5 ($COCH_3$), 170.6 ($COCH_3$), 170.7 ($COCH_3$) ppm. $C_{27}H_{42}O_{10}Si$ (554.70): calcd. C 58.46, H 7.63; found C 58.18, H, 7.39.

Methyl 6,7-Di-*O*-acetyl-2-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-L-*glycero*-α-D-*manno*-heptopyranoside (6): Compound **3** (1.24 g, 3.12 mmol) was treated with TBDMSCl (939 mg, 6.23 mmol) in DMF (20 mL) in the presence of imidazole (531 mg, 7.80 mmol) for 4.5 h at room temp. The mixture was poured into water (80 mL) and extracted with EtOAc (40 mL). The aqueous solution was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. Open column chromatography of the residue (hexane/EtOAc, 1:2) gave the title compound **6** (1.50 g, 94%) as a syrup. $[\alpha]_D^{25} = +8$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 0.11, 0.12 [s, 3 H each, Si(CH_3)$_2$C(CH$_3$)$_3$], 0.92 [s, 9 H, Si(CH$_3$)$_2$C(CH_3)$_3$], 2.05 (s, 3 H, COCH_3), 2.14 (s, 3 H, COCH_3), 2.71 (br. s, 1 H, 4-O*H*), 4.66, 4.82 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.25−7.36 (m, 5 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = −4.6, −4.5 [Si(CH_3)$_2$C(CH$_3$)$_3$], 18.3 [Si(CH$_3$)$_2$C(CH_3)$_3$], 25.9 [Si(CH$_3$)$_2$$C$(CH$_3$)$_3$], 20.8 (CO$CH_3$), 20.9 (CO$CH_3$), 55.0 (O$CH_3$), 73.4 ($CH_2$-Ph), 127.5, 127.7 (2 C), 128.2 (2 C), 138.4 (aromatic *C*), 170.5 ($COCH_3$), 171.8 ($COCH_3$) ppm. $C_{25}H_{40}O_9Si$ (512.67): calcd. C 58.57, H 7.86; found C 58.23, H 7.82.

Methyl 4,6,7-Tri-*O*-acetyl-2-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-L-*glycero*-α-D-*manno*-heptopyranoside (7): Compound **6** (145 mg, 0.283 mmol) was acetylated with Ac_2O/pyridine (2:1, v/v, 3 mL) containing a catalytic amount of DMAP at room temp. for 22 h. The reaction mixture was concentrated to a syrup that was purified by flash column chromatography to give the title compound **7** (154 mg, 97%) as an oil. $[\alpha]_D^{24} = +10$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 0.07, 0.07 [s, 3 H each, Si(CH_3)$_2$C(CH$_3$)$_3$], 0.88 [s, 9 H, Si(CH$_3$)$_2$C(CH_3)$_3$], 2.04 (s, 6 H, 2 COCH_3), 2.10 (s, 3 H, COCH_3), 3.32 (OCH_3), 4.64, 4.93 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.26−7.40 (m, 5 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = −5.1, −4.3 [Si(CH_3)$_2$C(CH$_3$)$_3$], 17.9 [Si(CH$_3$)$_2$C(CH_3)$_3$], 25.6 [Si(CH$_3$)$_2$$C$(CH$_3$)$_3$], 20.75 (CO$CH_3$), 20.83 (CO$CH_3$), 21.1 (CO$CH_3$), 55.1 (O$CH_3$), 73.7 ($CH_2$-Ph), 127.5,

127.7 (2 C), 128.2 (2 C), 138.4 (aromatic *C*), 169.4 (*C*OCH$_3$), 170.6 (*C*OCH$_3$), 170.7 (*C*OCH$_3$) ppm. $C_{27}H_{42}O_{10}Si$ (554.70): calcd. C 58.46, H 7.63; found C 58.22, H 7.47.

Methyl 4,6,7-Tri-*O*-acetyl-2-*O*-benzyl-L-*glycero*-α-D-*manno*-heptopyranoside (8): (a) Compound **5** (89 mg, 0.160 mmol) was treated with a solution of 1% (w/v) I_2 in MeOH[22] (4 mL) at room temp. for 50 min. The mixture was poured into an aqueous solution of $Na_2S_2O_3$ (10 mL) and then extracted with EtOAc (3 × 10 mL). Purification by flash column chromatography (hexane/EtOAc, 1:1) gave the title compound **8** (63 mg, 88%) as a colorless syrup. Compound **7** (24 mg, 0.043 mmol) was also treated with 1% (w/v) I_2 in MeOH (2 mL) at room temp. Even after 7 days, however, TLC (hexane/EtOAc, 2:1) showed that de-*O*-silylation was incomplete. No further attempts at optimizing this reaction or characterizing the reaction products were carried out. (b) Compound **7** (114 mg, 0.206 mmol) was treated with TFA/water[24] (9:1, v/v, 5 mL) at room temp. for 20 min. The mixture was concentrated to a residue, using toluene as an azeotrope, that was purified by flash column chromatography (hexane/EtOAc, 1:1) to give the title compound **8** (84 mg, 93%) as a colorless syrup. (c) Glacial acetic acid (143 μL, 2.50 mmol) and TBAF (1 M in THF; 1.25 mL, 1.25 mmol)[23] were added sequentially to a solution of compound **7** (139 mg, 0.250 mmol) in THF (2 mL). After stirring for 1 day at room temp., TBAF (1 M in THF; 0.63 mL, 2.5 molar equiv.) was added. The reaction was stopped by quenching with water after stirring for 10 days at room temp. The usual workup, followed by flash column chromatography (toluene/acetone, 9:1), gave the title compound **8** (76 mg, 67%). (d) Compound **3** (301 mg, 0.756 mmol) was stirred in pyridine (3 mL) containing TESCl (253 μL, 1.51 mmol) for 30 min at 0 °C. After performing the workup as described for **4**, the reaction mixture was acetylated with Ac_2O/pyridine (1:2, v/v, 9 mL) at room temp. for 2 days. The mixture was concentrated by coevaporation with toluene. The residue was treated with TFA/water (9:1, v/v, 10 mL) for 15 min at room temp. and concentrated as described in (b). Purification by flash column chromatography (CH_2Cl_2/acetone, 14:1) gave the title compound **8** as a colorless foam (304 mg, 91%).Compound **8**: $[\alpha]_D^{24} = -40$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 2.05 (s, 3 H, COCH_3), 2.07 (s, 3 H, COCH_3), 2.11 (s, 3 H, COCH_3), 2.27 (d, $^3J_{3\text{-OH,H-3}}$ = 11.0 Hz, 1 H, 3-O*H*), 3.34 (s, 3 H, OCH_3), 4.58, 4.77 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.26−7.37 (m, 5 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 20.7 (2 C, 2 CO*C*H$_3$), 20.9 (CO*C*H$_3$), 55.2 (O*C*H$_3$), 73.0 (*C*H$_2$-Ph), 127.8 (2 C), 128.1, 128.6 (2 C), 137.4 (aromatic *C*), 170.4 (*C*OCH$_3$), 170.5 (*C*OCH$_3$), 170.9 (*C*OCH$_3$) ppm. HR-ES-IMS: calcd. for $C_{21}H_{28}O_{10}Na$ [M + Na]$^+$: 463.1580; found 463.1562.

(2′*S*,3′*S*)-Methyl 6,7-Di-*O*-acetyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-*glycero*-α-D-*manno*-heptopyranoside (9): Compound **2** (1.10 g, 2.15 mmol) was dissolved in EtOAc (50 mL) and 10% Pd/C (0.3 g) was added. The mixture was hydrogenated under atmospheric pressure of hydrogen for 1 day and then filtered through Celite. The filtrate was evaporated to a syrup that was purified by open column chromatography (hexane/EtOAc, 2:1 → 1:2) to give the title compound **9** (0.88 g, 97%) as a foam. $[\alpha]_D^{25} = +165$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 1.27, 1.31 (s, 3 H each, BDA-CH_3), 2.05 (s, 3 H, COCH_3), 2.12 (s, 3 H, COCH_3), 2.34 (br. s, 1 H, 2-O*H*), 3.15, 3.27 (s, 3 H each, BDA-OCH_3), 3.35 (s, 3 H, OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 17.7, 17.8 (BDA-*C*H$_3$), 20.7 (CO*C*H$_3$), 21.0 (CO*C*H$_3$), 47.8, 48.1 (BDA-O*C*H$_3$), 54.9 (O*C*H$_3$), 100.1, 100.5 (BDA-C_q), 170.8 (*C*OCH$_3$), 170.4 (*C*OCH$_3$) ppm. HR-FABMS: calcd. for $C_{18}H_{30}O_{11}Na$ [M + Na]$^+$: 445.1685; found 445.1678.

(2′*S*,3′*S*)-Methyl (6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α- and β-D-glucopyranosyl)-(1→2)-6,7-di-*O*-acetyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-L-*glycero*-α-D-*manno*-heptopyranosides (11a,b): Glycosylation of **9** with **10**: TMSOTf was added at room temp. to a stirred mixture of the acceptor **9**, the donor **10**,[25] and molecular sieves (AW-300, 0.5 g) in either 1,4-dioxane or Et_2O (10 mL). Although TLC monitoring (hexane/toluene/EtOAc, 3:2:2) showed the complete consumption of the donor **10** after 10 min, the mixture was stirred for 1 h and then the reaction was terminated by the addition of triethylamine. The mixture was diluted with EtOAc (30 mL) and filtered through Celite. The filtrate was washed with water (30 mL) and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (hexane/toluene/EtOAc, 3:2:2) of the residue gave the α-(1→2)-linked **11a**, the β-(1→2)-linked **11b**, *N*-(6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxyl-β-D-glucopyranosyl)trichloroacetamide (**12**), (2′*S*,3′*S*)-methyl 6,7-di-*O*-acetyl-3,4-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-2-*O*-trimethylsilyl-L-*glycero*-α-D-*manno*-heptopyranoside (**13**), and the unreacted acceptor **9**. Compound **11a**, which co-eluted with both trichloroacetamide [$Cl_3CC(=O)NH_2$] and the donor hydrolysate, was purified as follows. Most of trichloroacetamide of the mixture was removed after crystallization (CH_2Cl_2/hexane) and filtration, and the donor hydrolysate was removed after acetylation (Ac_2O/pyridine) of the resulting mixture and subsequent flash column chromatography (hexane/toluene/EtOAc, 3:2:2). The β-anomer **11b** was crystallized from EtOAc/hexane. Both the *N*-glycoside **12** and the 2-*O*-trimethylsilylated acceptor **13** were re-purified by flash column chromatography (toluene/hexane/EtOAc, 6:2:1, and toluene/EtOAc, 10:1, respectively). (a) Using 0.04 molar equiv. of TMSOTf in 1,4-dioxane: Glycosylation of the acceptor **9** (203 mg, 0.480 mmol) with the donor **10** (441 mg, 0.771 mmol) in 1,4-dioxane (10 mL) in the presence of TMSOTf (6 μL, 0.033 mmol) gave **11a** (91 mg, 23%), **11b** (23 mg, 6%), the *N*-glycoside **12** (71 mg, 16%: based on the donor), and the acceptor **9** (129 mg, 63%). (b) Using 0.2 molar equiv. of TMSOTf in 1,4-dioxane: Glycosylation of **9** (200 mg, 0.473 mmol) with **10** (433 mg, 0.758 mmol) in 1,4-dioxane (10 mL) in the presence of TMSOTf (27 μL, 0.152 mmol) gave **11a** (104 mg, 26%), **11b** (26 mg, 7%), the *N*-glycoside **12** (21 mg, 5%), the 2-*O*-trimethylsilylated acceptor **13** (33 mg, 14%), and the acceptor **9** (97 mg, 48%). (c) Using 0.04 molar equiv. of TMSOTf in Et_2O: Glycosylation of **9** (208 mg, 0.492 mmol) with **10** (450 mg, 0.787 mmol) in Et_2O (10 mL) in the presence of TMSOTf (6 μL, 0.033 mmol) gave **11a** (236 mg, 58%), **11b** (89 mg, 22%), the *N*-glycoside **12** (35 mg, 8%), and the acceptor **9** (23 mg, 11%). (d) Using 0.2 molar equiv. of TMSOTf in Et_2O: Glycosylation of 9 (205 mg, 0.485 mmol) with **10** (445 mg, 0.778 mmol) in Et_2O (10 mL) in the presence of TMSOTf (28 μL, 0.156 mmol) gave **11a** (225 mg, 56%), **11b** (84 mg, 21%), the *N*-glycoside **12** (40 mg, 9%), the 2-*O*-trimethylsilylated acceptor **13** (33 mg, 14%), and the acceptor **9** (9 mg, 4%).

Compound 11a: $[\alpha]_D^{24} = +149$ (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 1.27, 1.29 (s, 3 H each, BDA-CH_3), 2.05 (s, 9 H, 2 COCH_3), 2.05 (s, 3 H, COCH_3), 3.13, 3.25 (s, 3 H each, BDA-OCH_3), 3.33 (s, 3 H, OCH_3), 4.58, 4.86 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.87, 4.90 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 7.26−7.39 (m, 10 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz,

$CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 17.6, 17.8 (BDA-*C*H_3), 20.7 (CO*C*H_3), 20.8 (CO*C*H_3), 47.9, 48.0 (BDA-O*C*H_3), 54.7 (O*C*H_3), 75.1 (*C*H_2-Ph), 75.2 (*C*H_2-Ph), 99.9, 100.5 (BDA-C_q), 127.9−128.5, 137.5, 137.8 (aromatic *C*), 170.38 (*C*OCH_3), 170.41 (*C*OCH_3), 170.6 (*C*OCH_3) ppm. FAB-HRMS: calcd. for $C_{40}H_{53}O_{16}N_3Na$ [M + Na]$^+$ 854.3324; found 854.3334.

Compound 11b: M.p. 157−158°. $[\alpha]_D^{21}$ = +82 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 1.25, 1.27 (s, 3 H each, BDA-C*H*$_3$), 1.99 (s, 3 H, COC*H*$_3$), 2.04 (s, 3 H, COC*H*$_3$), 2.08 (s, 3 H, COC*H*$_3$), 3.11, 3.26 (s, 3 H each, BDA-OC*H*$_3$), 3.35 (s, 3 H, OC*H*$_3$), 4.57, 4.84 (d, ^2J = 11.0 Hz, 1 H each, C*H*$_2$-Ph), 4.81, 4.91 (d, ^2J = 11.0 Hz, 1 H each, C*H*$_2$-Ph), 7.25−7.40 (m, 10 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 17.75, 17.84 (BDA-*C*H_3), 20.70 (CO*C*H_3), 20.73 (CO*C*H_3), 20.8 (CO*C*H_3), 47.6, 48.0 (BDA-O*C*H_3), 54.9 (O*C*H_3), 75.0 (*C*H_2-Ph), 75.4 (*C*H_2-Ph), 99.8, 100.2 (BDA-C_q), 128.0−128.5, 137.5, 137.8 (aromatic *C*), 170.3 (*C*OCH_3), 170.4 (*C*OCH_3), 170.5 (*C*OCH_3) ppm. FAB-HRMS: calcd. for $C_{40}H_{53}O_{16}N_3Na$ [M + Na]$^+$ 854.3324; found 854.3345.

***N*-Glycoside 12:** $[\alpha]_D^{26}$ = +29 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.04 (s, 3 H, COC*H*$_3$), 3.62 (t, $^3J_{4,5}$ = 8.5 Hz, 1 H, H-4), 3.66 (t, $^3J_{3,4}$ = 8.5 Hz, 1 H, H-3), 3.75 (dddd, 1 H, H-5), 3.92 (dd, $^3J_{2,3}$ = 9.5 Hz, 1 H, H-2), 4.28 (d, $^3J_{5,6}$ = 3.5 Hz, 2 H, H-6a and 6b), 4.59, 4.83 (d, ^2J = 11.0 Hz, 1 H each, C*H*$_2$-Ph), 4.89, 4.92 (d, ^2J = 11.0 Hz, 1 H each, C*H*$_2$-Ph), 5.63 (dd, $^3J_{1,2}$ = 5.5 Hz, 1 H, H-1), 7.02 (d, $J_{NH,H-1}$ = 6.5 Hz, 1 H, N*H* $COCCl_3$), 7.28−7.38 (m, 10 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 (CO*C*H_3), 61.7 (C-2), 62.3 (C-6), 70.8 (C-5), 75.2 (*C*H_2-Ph), 75.7 (*C*H_2-Ph), 76.97 (C-4), 77.02 (C-1), 81.1 (C-3), 92.0 (NHCO*C*Cl_3), 128.1 (2 C), 128.2 (2 C), 128.3, 128.4, 128.6 (2 C), 128.7 (2 C), 136.85, 136.89 (aromatic *C*), 161.8 (NH*C*OCCl_3), 170.5 (*C*OCH_3) ppm. HR-ESIMS: calcd. for $C_{24}H_{25}Cl_3NO_6Na$ [M + Na]$^+$: 593.0737, found 593.0749.

2-*O*-Trimethylsilylated Acceptor 13: $[\alpha]_D^{26}$ = +115 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.15 [s, 1 H, Si(CH_3)$_3$], 1.25, 1.28 (s, 3 H each, BDA-C*H*$_3$), 2.04 (s, 3 H, COC*H*$_3$), 2.13 (s, 3 H, COC*H*$_3$), 3.11, 3.26 (s, 3 H each, BDA-OC*H*$_3$), 3.32 (s, 3 H, OC*H*$_3$), 3.89 (m, $^3J_{2,3}$ = 3.0 Hz, 1 H, H-2), 3.90 (dd, $^3J_{3,4}$ = 9.5 Hz, 1 H, H-3), 3.92 (dd, $^3J_{5,6}$ = 2.0 Hz, 1 H, H-5), 4.00 (t, $^3J_{4,5}$ = 9.5 Hz, 1 H, H-4), 4.27 (dd, $^2J_{7a,7b}$ = 11.0 Hz, 1 H, H-7a), 4.33 (dd, 1 H, H-7b), 4.67 (s, 1 H, H-1), 5.44 (ddd, $^3J_{6,7a}$ = 8.0, $^3J_{6,7b}$ = 7.0 Hz, 1 H, H-6) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 0.4 [Si(*C*H_3)$_3$], 17.7, 17.8 (BDA-*C*H_3), 20.7 (CO*C*H_3), 20.9 (CO*C*H_3), 47.4, 47.9 (BDA-O*C*H_3), 54.7 (O*C*H_3), 61.6 (C-7), 62.0 (C-4), 67.7 (C-6), 68.2 (C-3), 68.8 (C-5), 70.4 (C-2), 99.6, 100.0 (BDA-C_q), 102.8 (C-1), 170.2 (*C*OCH_3), 170.4 (*C*OCH_3) ppm. HR-ESIMS: calcd. for $C_{21}H_{38}O_{11}SiNa$ [M + Na]$^+$: 517.2081; found 517.2064.

Methyl (6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→2)-6,7-di-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranoside (14): Compound **11a** (685 mg, 0.823 mmol) was treated with TFA/water (9:1, v/v, 10 mL) at room temp. for 15 min. The reaction mixture was co-evaporated with toluene to give an oil. Purification of the oil by flash column chromatography (CH_2Cl_2/acetone, 9:1 → 6:1) gave the title compound **14** (563 mg, 95%) as a foam. $[\alpha]_D^{20}$ = +41 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 2.06 (s, 3 H, COC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$), 2.91 (d, $^3J_{3\text{-OH},H-3}$ = 8.0 Hz, 1 H, 3-O*H*), 3.13 (d, $^3J_{4\text{-OH},H-4}$ = 3.5 Hz, 1 H, 4-O*H*), 3.34 (s, 3 H, OC*H*$_3$), 4.58, 4.86 (d, ^2J = 11.0 Hz, 1 H each, C*H*$_2$-Ph), 4.87 (m, 2 H, C*H*$_2$-Ph), 7.26−7.38 (m, 10 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 20.7 (CO*C*H_3), 20.8 (CO*C*H_3), 55.1 (O*C*H_3), 75.3 (*C*H_2-Ph), 75.6 (*C*H_2-Ph), 128.5−128.6, 137.2, 137.3 (aromatic *C*), 170.4 (*C*OCH_3), 170.5 (*C*OCH_3), 170.8 (*C*OCH_3) ppm. HR-FABMS: calcd. for $C_{34}H_{43}O_{14}N_3Na$ [M + Na]$^+$: 740.2643; found 740.2659.

Methyl (6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→2)-4,6,7-tri-*O*-acetyl-3-*O*-triethylsilyl-L-*glycero*-α-D-*manno*-heptopyranoside (15): Compound **14** (563 mg, 0.784 mmol) was dissolved in pyridine (10 mL) and cooled in an ice-water bath. TESCl (392 μL, 2.34 mmol) was added at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to room temp. and stirred for 30 min. The reaction mixture was quenched with water and then extracted with EtOAc. The combined extracts were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated to give an oil that was acetylated with Ac_2O/pyridine (1:2, v/v, 15 mL) at room temp. for 3 days. The reaction mixture was concentrated to a syrup that was purified by flash column chromatography (hexane/EtOAc, 2:1) to give the title compound **15** (603 mg, 88%) as a syrup. $[\alpha]_D^{27}$ = +71 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 0.55−0.67 [m, 6 H, Si(CH_2CH$_3$)$_3$], 0.96 [m, 9 H, Si(CH$_2$CH_3)$_3$], 2.01 (s, 3 H, COC*H*$_3$), 2.04 (s, 3 H, COC*H*$_3$), 2.04 (s, 3 H, COC*H*$_3$), 2.05 (s, 3 H, COC*H*$_3$), 3.35 (s, 3 H, OC*H*$_3$), 4.57, 4.87 (d, ^2J = 11.0 Hz, 1 H each, C*H*$_2$-Ph), 4.88, 4.93 (d, ^2J = 10.5 Hz, 1 H each, C*H*$_2$-Ph), 7.26−7.40 (m, 10 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 4.8 [Si(*C*H$_2$CH$_3$)$_3$], 6.6 [Si(CH$_2$*C*H$_3$)$_3$], 20.6 (CO*C*H_3), 20.7 (CO*C*H_3), 20.8 (CO*C*H_3), 20.9 (CO*C*H_3), 55.2 (O*C*H_3), 75.2 (*C*H_2-Ph), 75.3 (*C*H_2-Ph), 127.9−128.5, 137.4, 137.8 (aromatic *C*), 169.1 (*C*OCH_3), 170.5 (*C*OCH_3), 170.6 (*C*OCH_3), 170.7 (*C*OCH_3) ppm. HR-FABMS: calcd. for $C_{42}H_{59}O_{15}N_3SiNa$ [M + Na]$^+$: 896.3613; found 869.3625.

Methyl (6-*O*-Acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl)-(1→2)-4,6,7-tri-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranoside (16): Compound **15** (597 mg, 0.683 mmol) was hydrolyzed with TFA/water (9:1, v/v, 10 mL) at room temp. for 5 min. The mixture was concentrated to a residue that was purified by open column chromatography (EtOAc/hexane, 1:1) to give the title compound **16** (512 mg, 99%) as a syrup. Alternatively, compound **16** was prepared as follows: Compound **14** (408 mg, 0.568 mmol) was treated with TESCl (285 μL, 1.70 mmol) in pyridine (10 mL) at 0 °C for 1 h and then acetylated in a similar manner described for **15**. Hydrolysis of the acetylated mixture in TFA/water (9:1, v/v, 10 mL) for 5 min, and subsequent purification by flash column chromatography (CH_2Cl_2/acetone, 14:1), gave **16** as a colorless foam (381 mg, 88%). $[\alpha]_D^{25}$ = +13 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 1): δ = 2.00 (s, 3 H, COC*H*$_3$), 2.05 (s, 3 H, COC*H*$_3$), 2.06 (s, 3 H, COC*H*$_3$), 2.10 (s, 3 H, COC*H*$_3$), 2.94 (d, $^3J_{3\text{-OH},H-3}$ = 11.5 Hz, 1 H, 3-O*H*), 3.35 (s, 3 H, OC*H*$_3$), 4.59, 4.87 (d, ^2J = 10.5 Hz, 1 H each, C*H*$_2$-Ph), 4.91 (m, 2 H, C*H*$_2$-Ph), 7.26−7.40 (m, 10 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 2): δ = 20.5 (CO*C*H_3), 20.7 (CO*C*H_3), 20.8 (CO*C*H_3), 20.9 (CO*C*H_3), 55.2 (O*C*H_3), 75.3 (*C*H_2-Ph), 75.8 (*C*H_2-Ph), 127.1−128.6, 137.2, 137.3 (aromatic *C*), 170.3 (*C*OCH_3), 170.5 (2 C, 2 *C*OCH_3), 170.8 (*C*OCH_3) ppm. HR-FABMS: calcd. for $C_{36}H_{45}N_3O_{15}Na$ [M + Na]$^+$: 782.2748; found 782.2769.

Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzyl-α- and β-D-glucopyranosyl)-(1→3)-[6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1→2)]-4,6,7-tri-*O*-

acetyl-L-*glycero*-α-D-*manno*-heptopyranosides (18a,b): Glycosylation of **16** with the per-*O*-benzylated lactosyl trichloroacetimidate **17**: The acceptor **16** was treated with **17**[14] in a similar manner described for the synthesis of **11a**. Although TLC monitoring of each glycosylation mixture showed no significant changes in the pattern of the reaction products after 20 min, the mixture was stirred for 0.5−6 h at room temp. The tetrasaccharides and disaccharides of each glycosylation mixture were separated by gel permeation chromatography [Sephadex LH-20 (2.6 × 80 cm, $CHCl_3$/MeOH, 1:1)]. Purification of a mixture containing the tetrasaccharides by flash column chromatography (hexane/EtOAc, 1:1) gave α-(1→3)-linked **18a** and β-(1→3) **18b**. Similarly, flash column chromatography (hexane/EtOAc, 6:1) of a mixture containing the disaccharides gave the unreacted acceptor **16** and *N*-(2,3,4,6-*tert*a-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzyl-β-D-glucopyranosyl)trichloroacetamide (**19**). (a) Using 0.04 molar equiv. of TMSOTf in 1,4-dioxane: Glycosylation of the acceptor **16** (145 mg, 0.19 mmol) with the donor **17** (403 mg, 0.36 mmol) in 1,4-dioxane (10 mL) in the presence of TMSOTf (0.14 M in 1,4-dioxane, 102 μL, 0.014 mmol) for 6 h at room temp. gave the α-linked compound **18a** (87 mg, 27%), the β-linked compound **18b** (9 mg, 3%), and the unchanged acceptor **16** (97 mg, 67%). (b) Using 0.2 molar equiv. of TMSOTf in 1,4-dioxane: Glycosylation of **16** (121 mg, 0.159 mmol) with **17** (443 mg, 0.396 mmol) in 1,4-dioxane (10 mL) in the presence of TMSOTf (0.55 M in 1,4-dioxane, 143 μL, 0.079 mmol) for 30 min at room temp. gave the α-linked compound **18a** (159 mg, 58%), the β-linked compound **18b** (16 mg, 6%), the *N*-glycoside **19** (56 mg, 13%: based on the donor), and the unreacted acceptor **16** (34 mg, 28%). (c) Using 0.04 molar equiv. of TMSOTf in Et_2O: Glycosylation of **16** (121 mg, 0.159 mmol) with **17** (443 mg, 0.396 mmol) in Et_2O (6 mL) in the presence of TMSOTf (0.14 M in Et_2O, 147 μL, 0.016 mmol) for 30 min at room temp. gave the α-linked compound **18a** (210 mg, 77%), the β-linked compound **18b** (21 mg, 8%), the *N*-glycoside **19** (143 mg, 32%), and the unreacted acceptor **16** (12 mg, 10%). (d) Using 0.2 molar equiv. of TMSOTf in Et_2O: Glycosylation of **16** (459 mg, 0.604 mmol) with **17** (1.66 g, 1.49 mmol) in Et_2O (15 mL) in the presence of TMSOTf (54 μL, 0.30 mmol) and molecular sieves (AW-300, 2.0 g) for 1 h at room temp. gave the α-linked compound **18a** (771 mg, 74%), the β-linked compound **18b** (103 mg, 10%), and the unreacted acceptor **16** (34 mg, 7%).

Compound 18a: $[\alpha]_D^{23} = +30$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 5): δ = 1.73 (s, 3 H, COCH_3), 1.98 (s, 3 H, COCH_3), 2.04 (s, 6 H, 2 COCH_3), 3.28 (s, 3 H, OCH_3), 4.15, 4.30 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.33, 4.41 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.52, 4.96 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.55, 4.84 (d, ^2J = 10.5 Hz, 1 H each, CH_2-Ph), 4.62, 5.08 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.64, 4.76 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.67, 4.71 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.85, 4.93 (d, ^2J = 10.5 Hz, 1 H each, CH_2-Ph), 4.87, 4.93 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 7.05−7.36 (m, 45 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 6): δ = 20.5 (CO*C*H$_3$), 20.6 (CO*C*H$_3$), 20.7 (CO*C*H$_3$), 20.8 (CO*C*H$_3$), 55.2 (O*C*H$_3$), 72.5 (*C*H$_2$-Ph), 73.29 (*C*H$_2$-Ph), 73.33 (*C*H$_2$-Ph), 73.5 (*C*H$_2$-Ph), 74.5 (*C*H$_2$-Ph), 74.9 (*C*H$_2$-Ph), 75.1 (2 C, 2 *C*H$_2$-Ph), 75.2 (*C*H$_2$-Ph), 125.2−129.0, 137.4, 137.7, 138.0, 138.3, 138.4. 138.7, 138.97, 139.01, 139.5 (aromatic *C*), 169.3 (*C*OCH$_3$), 170.42 (*C*OCH$_3$), 170.46 (*C*OCH$_3$), 170.52 (*C*OCH$_3$) ppm. FAB-HRMS: calcd. for $C_{97}H_{107}O_{25}N_3Na$ [M + Na]$^+$ 1736.7091; found 1736.7126.

Compound 18b: $[\alpha]_D^{23} = +33$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 5): δ = 1.93 (s, 3 H, COCH_3), 2.00 (s, 3 H, COCH_3), 2.03 (s, 3 H, COCH_3), 2.04 (s, 3 H, COCH_3), 3.30 (s, 3 H, OCH_3), 4.21, 4.30 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.40, 4.46 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.49, 4.79 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.53, 4.94 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.63, 5.01 (d, ^2J = 10.5 Hz, 1 H each, CH_2-Ph), 4.67, 4.72 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.67, 4.72 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.78, 4.82 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.87, 4.93 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 7.02−7.39 (m, 45 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 6): δ = 20.6 (CO*C*H$_3$), 20.70 (2 C, 2 CO*C*H$_3$), 20.74 (CO*C*H$_3$), 55.1 (O*C*H$_3$), 72.5 (*C*H$_2$-Ph), 72.8 (*C*H$_2$-Ph), 73.3 (*C*H$_2$-Ph), 74.1 (*C*H$_2$-Ph), 74.6 (*C*H$_2$-Ph), 74.9 (*C*H$_2$-Ph), 75.0 (2 C, 2 *C*H$_2$-Ph), 75.1 (*C*H$_2$-Ph), 126.6−128.4, 137.4, 137.8, 138.0, 138.2, 138.4, 138.6, 138.9, 139.0 (2 C) (aromatic *C*), 169.4 (*C*OCH$_3$), 170.43 (*C*OCH$_3$), 170.46 (*C*OCH$_3$), 170.50 (*C*OCH$_3$) ppm. FAB-HRMS: calcd. for $C_{97}H_{107}O_{25}N_3Na$ [M + Na]$^+$: 1736.7091; found 1736.7075. ***N*-Glycoside 19:** $[\alpha]_D^{25} = +32$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.37 (dd, $^3J_{3^{II},4^{II}} = 3.0$ Hz, 1 H, H-3^{II}), 3.37 (m, $^3J_{5^{II},6^{II}a} = 5.0$, $^3J_{5^{II},6^{II}b} = 6.5$ Hz, 1 H, H-5^{II}), 3.53 (dd, $^2J_{6^{II}a,6^{II}b} = 11.5$ Hz, 1 H, H-6^{II}a), 3.55 (dd, 1 H, H-6^{II}b), 3.57 (dd, $^2J_{6^{I}a,6^{I}b} = 11.0$ Hz, 1 H, H-6^{I}a), 3.65 (dddd, $^3J_{5^{I},6^{I}a} = 2.5$, $^3J_{5^{I},6^{I}b} = 3.5$ Hz, 1 H, H-5^{I}), 3.73 (t, $^3J_{3^{I},4^{I}} = 7.0$ Hz, 1 H, H-3^{I}), 3.74 (dd, $^3J_{2^{II},3^{II}} = 9.8$ Hz, 1 H, H-2^{II}), 3.76 (dd, $^3J_{2^{I},3^{I}} = 7.5$ Hz, 1 H, H-2^{I}), 3.79 (dd, 1 H, H-6^{I}b), 3.90 (d, 1 H, H-4^{II}), 4.01 (dd, $^3J_{4^{I},5^{I}} = 9.0$ Hz, 1 H, H-4^{I}), 4.29, 4.37 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.36 (d, $^3J_{1^{II},2^{II}} = 7.5$ Hz, 1 H, H-1^{II}), 4.36, 4.53 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.51, 4.71 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.56, 4.97 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.64, 4.94 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.70, 4.71 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.73, 4.76 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 5.53 (dd, $^3J_{1^{I},2^{I}} = 4.5$ Hz, 1 H, H-1^{I}), 7.14−7.35 (m, 35 H, aromatic *H*), 7.47 (d, $^3J_{NH,H\text{-}1^{I}} = 6.5$ Hz, 1 H, N*H* COCCl$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 67.9 (C-6^{I}), 68.3 (C-6^{II}), 72.4 (C-5^{I}), 72.7 (*C*H$_2$-Ph), 73.0 (*C*H$_2$-Ph), 73.1 (C-5^{II}), 73.2, 73.4 (*C*H$_2$-Ph), 73.6 (C-4^{II}), 74.5 (*C*H$_2$-Ph), 74.7 (*C*H$_2$-Ph), 75.2 (*C*H$_2$-Ph), 75.8 (C-2^{I}), 76.5 (C-1^{I}), 78.8 (C-3^{I}), 79.7 (C-2^{II}), 82.4 (C-3^{II}), 92.5 (NHCO*C*Cl$_3$), 103.2 (C-1^{II}), 127.4−128.5, 137.0, 138.0, 138.1, 1*3*8.4, 138.5, 138.6, 138.9 (aromatic *C*), 161.9 (NH*C*OCCl$_3$) ppm. HR-ESIMS: calcd. for $C_{63}H_{64}Cl_3NO_{11}Na$ [M + Na]$^+$: 1138.3443; found 1138.3448.

Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)- and (1→4)-[6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1→2)]-6,7-di-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranosides (20, 21): Glycosylation of the acceptor **14** (103 mg, 0.144 mmol) with the donor **17** (267 mg, 0.239 mmol) in 1,4-dioxane (10 mL) in the presence of molecular sieves (AW-300, 0.5 g) and TMSOTf (0.14 M in 1,4-dioxane, 70 μL, 0.0096 mmol) for 2 h gave the α-(1→3)-linked tetrasaccharide **20** (56 mg, 24%), the α-(1→4)-linked tetrasaccharide **21** (66 mg, 28%), and the unreacted acceptor **14** (21 mg, 21%). In addition to **20** and **21**, a mixture of tetrasaccharides, presumably β-(1→3)- and β-(1→4)-linked products (38 mg, 16%) was obtained, but these products were not further characterized because of the complexity of their 2D spectra.

The α-(1→3)-Linked Tetrasaccharide 20: $[\alpha]_D^{23} = +49$ ($c = 1.0$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 5): δ = 2.00 (s, 3 H, COCH_3), 2.02 (s, 3 H, COCH_3), 2.05 (s, 3 H, COCH_3), 3.31 (s, 3 H, OCH_3), 3.67 (d, $^3J_{4\text{-}OH,H\text{-}4} = 2.0$ Hz, 1 H, 4-O*H*), 4.20, 4.36 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.33, 4.47 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.53, 4.97 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.68, 4.71 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.68, 4.84 (d, ^2J =

11.0 Hz, 1 H each, CH_2-Ph), 4.69, 5.14 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.82, 4.89 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.84, 4.87 (d, ^2J = 12.5 Hz, 1 H each, CH_2-Ph), 7.10−7.37 (m, 45 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 6): δ = 20.7 (3 C, 3 CO*C*H_3), 55.0 (O*C*H_3), 72.5 (*C*H_2-Ph), 73.3 (*C*H_2-Ph), 73.4 (*C*H_2-Ph), 74.1 (*C*H_2-Ph), 74.6 (*C*H_2-Ph), 74.92 (*C*H_2-Ph), 74.93 (*C*H_2-Ph), 75.2 (*C*H_2-Ph), 75.4 (*C*H_2-Ph), 126.9−128.5, 137.3, 137.6, 137.7, 138.0, 138.2, 138.5, 139.0 (2 C), 139.4 (aromatic *C*), 170.5 (2 C, 2 *C*OCH$_3$), 170.5 (*C*OCH$_3$) ppm. FAB-HRMS: calcd. for $C_{95}H_{105}O_{24}N_3Na$ [M + Na]$^+$: 1694.6986; found 1694.6976.

The α-(1→4)-Linked Tetrasaccharide 21: $[\alpha]_D^{23}$ = +78 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 5): δ = 1.79 (s, 3 H, COCH_3), 1.98 (s, 3 H, COCH_3), 2.05 (s, 3 H, COCH_3), 3.31 (s, 3 H, OCH_3), 3.67 (d, $^3J_{3\text{-OH,H-3}}$ = 2.0 Hz, 1 H, 3-O*H*), 4.23, 4.39 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.36, 4.62 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.53, 4.96 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.58, 4.88 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.65, 4.68 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.65, 5.14 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.71, 4.84 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.74, 4.87 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.90, 4.88 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 7.12−7.41 (m, 45 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 6): δ = 20.5 (CO*C*H_3), 20.7 (CO*C*H_3), 20.8 (CO*C*H_3), 54.9 (O*C*H_3), 72.7 (*C*H_2-Ph), 73.1 (*C*H_2-Ph), 73.4 (*C*H_2-Ph), 74.57 (*C*H_2-Ph), 74.61 (*C*H_2-Ph), 75.2−75.3 (4 C, 4 *C*H_2-Ph), 127.0−128.6, 137.1, 137.3, 137.7, 138.25, 138.30, 138.6, 138.8, 139.1, 139.2 (aromatic *C*), 169.9 (*C*OCH$_3$), 170.2 (*C*OCH$_3$), 170.5 (*C*OCH$_3$) ppm. HR-FABMS: calcd. for $C_{95}H_{105}O_{24}N_3Na$ [M + Na]$^+$: 1694.6986; found 1694.6960.

Methyl (2,3,4,6-Tetra-*O*-benzyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl)-(1→3)-[2-acetamide-6-*O*-acetyl-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl-(1→2)]-4,6,7-tri-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranoside (22): (a) Using Lindlar catalyst:[33] A mixture of compound **18a** (771 mg, 0.450 mmol) and the catalyst [Pd (5%) on calcium carbonate; 2.0 g] in EtOAc (40 mL) was stirred vigorously for 3 days under an atmospheric pressure of hydrogen. The mixture was filtered through Celite and the filtrate was concentrated to dryness. The residue was dissolved in MeOH/Ac_2O (7:3, v/v, 20 mL) and stirred at room temp. for 1 h. The mixture was concentrated to a residue that was purified by flash column chromatography (hexane/EtOAc, 3:2 → 1:1) to give the title compound **22** (692 mg, 89%) as a foam. (b) Using AcSH/pyridine:[31] Compound **18a** (87 mg, 0.051 mmol) was treated with AcSH (2 mL) and pyridine (1 mL) at 40 °C for 12 days. The AcSH was evaporated under a stream of nitrogen and the residue was purified by flash column chromatography (hexane/toluene/EtOAc, 1:1:1) to give the title compound **22** (59 mg, 68%) as a colorless foam. (c) Zinc/AcOH:[32] A mixture of compound **18a** (52 mg, 0.030 mmol), glacial acetic acid (0.4 mL), and zinc powder (400 mg) was stirred in CH_2Cl_2 (5 mL) for 8 days at room temp. After filtering the mixture through Celite, the filtrate was treated with Ac_2O/MeOH (3:7, v/v, 5 mL) at room temp. for 1 h. The mixture was concentrated to a residue that was purified by flash column chromatography (hexane/EtOAc, 3:2 → 1:1) to give the title compound **22** (36 mg, 68%). Compound **22**: $[\alpha]_D^{23}$ = +36 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 5): δ = 1.84 (s, 3 H, COCH_3), 1.91 (s, 3 H, COCH_3), 1.97 (s, 3 H, COCH_3), 2.01 (s, 3 H, COCH_3), 2.04 (s, 3 H, COCH_3), 3.26 (s, 3 H, OCH_3), 4.16, 4.28 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.16, 4.29 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.50, 4.95 (d, ^2J = 11.5 Hz, 1 H each, CH_2-Ph), 4.54, 4.82 (d, ^2J = 10.5 Hz, 1 H each, CH_2-Ph), 4.58, 5.06 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.63, 4.72 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.66, 4.78 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 4.68, 4.71 (d, ^2J = 12.0 Hz, 1 H each, CH_2-Ph), 4.76, 4.85 (d, ^2J = 11.0 Hz, 1 H each, CH_2-Ph), 6.32 (d, $^3J_{NH,H}$ = 4.0 Hz, 1 H, N*H*Ac), 7.09−7.34 (m, 45 H, aromatic *H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 6): δ = 20.6 (CO*C*H_3), 20.7 (CO*C*H_3), 20.8 (CO*C*H_3), 23.4 (CO*C*H_3), 55.2 (O*C*H_3), 72.4 (*C*H_2-Ph), 73.1 (*C*H_2-Ph), 73.3 (*C*H_2-Ph), 73.9 (*C*H_2-Ph), 74.6 (*C*H_2-Ph), 74.9 (*C*H_2-Ph), 75.0 (*C*H_2-Ph), 75.1 (*C*H_2-Ph), 75.3 (*C*H_2-Ph), 126.9−128.5, 137.7, 137.9, 138.0, 138.1, 138.2, 138.4, 138.90, 138.93, 139.1 (aromatic *C*), 169.7 (*C*OCH$_3$), 170.35 (*C*OCH$_3$), 170.44 (*C*OCH$_3$), 170.61 (*C*OCH$_3$), 170.64 (*C*OCH$_3$) ppm. HR-FABMS: calcd. for $C_{95}H_{105}O_{24}N_3Na$ [M + Na]$^+$: 1694.6986; found 1694.6960.

Methyl (2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-(2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl)-(1→3)-[2-acetamide-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl-(1→3)]-4,6,7-tri-*O*-acetyl-L-*glycero*-α-D-*manno*-heptopyranoside (23): Compound **22** (692 mg, 0.400 mmol) was dissolved in EtOH/CH_2Cl_2 (4:1, v/v, 20 mL) and stirred with activated charcoal overnight. The mixture was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in MeOH/EtOAc/AcOH (2:1:0.1, v/v/v, 15 mL) and Pd/C (10%, 500 mg) was added. The mixture was hydrogenated (0.9 MPa) with vigorous stirring for 1.5 h. The mixture was filtered through Celite and the filtrate was concentrated to a residue. Acetylation of the residue with Ac_2O/pyridine (1:2, v/v, 12 mL) overnight at room temp., and subsequent flash column chromatography (EtOAc/hexane, 9:1), gave the title compound **23** (509 mg, 98%). $[\alpha]_D^{24}$ = +45 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$; data for the ring and the exocyclic protons are listed in Table 5): δ = 1.96 (s, 3 H, COCH_3), 1.99 (s, 3 H, COCH_3), 2.01 (s, 3 H, COCH_3), 2.02 (s, 3 H, COCH_3), 2.03 (s, 3 H, COCH_3), 2.06 (s, 6 H, 2 COCH_3), 2.09 (s, 3 H, COCH_3), 2.10 (s, 3 H, COCH_3), 2.11 (s, 3 H, COCH_3), 2.13 (s, 3 H, COCH_3), 2.15 (s, 3 H, COCH_3), 2.19 (s, 3 H, COCH_3), 3.37 (s, 3 H, OCH_3) 6.15 (d, $^3J_{NH,H}$ = 4.5 Hz, 1 H, N*H*Ac) ppm. ^{13}C NMR (125 MHz, $CDCl_3$; data for the skeletal carbon atoms are listed in Table 6): δ = 20.4−22.6 (CO*C*H_3), 55.3 (O*C*H_3), 169.08 (*C*OCH$_3$), 169.11 (*C*OCH$_3$), 169.2 (*C*OCH$_3$), 169.8 (*C*OCH$_3$), 169.95 (*C*OCH$_3$), 170.00 (*C*OCH$_3$), 170.19 (*C*OCH$_3$), 170.23 (*C*OCH$_3$), 170.40 (*C*OCH$_3$), 170.42 (*C*OCH$_3$), 170.45 (*C*OCH$_3$), 170.55 (*C*OCH$_3$), 170.64 (*C*OCH$_3$) ppm. HR-FABMS: calcd. for $C_{54}H_{76}NO_{35}$ [M + H]$^+$: 1298.4198; found 1298.4186.

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[1] A. Preston, R. E. Mandrell, B. W. Gibson, M. A. Apicella, *Crit. Rev. Microbiol.* **1996**, *22*, 139−180.
[2] R. Yamasaki, B. E. Bacon, W. Nasholds, H. Schneider, J. M. Griffiss, *Biochemistry* **1991**, *30*, 10566−10575.
[3] C. M. John, J. M. Griffiss, M. A. Apicella, R. E. Mandrell, B. W. Gibson, *J. Biol. Chem.* **1991**, *266*, 19303−19311.
[4] D. E. Kerwood, H. Schneider, R. Yamasaki, *Biochemistry* **1992**, *31*, 12760−12768.
[5] A. Gamian, M. Beurret, F. Michon, J. R. Brisson, H. J. Jennings, *J. Biol. Chem.* **1992**, *267*, 922−925.
[6] N. J. Phillips, M. A. Apicella, J. M. Griffiss, B. W. Gibson, *Biochemistry* **1992**, *31*, 4515−4526.
[7] A. F. M. Verheul, H. Snippe, J. T. Poolman, *Microbiol. Rev.* **1993**, *57*, 34−49.

[8] S. Gulati, D. P. McQuillen, J. Sharon, P. A. Rice, *J. Infect. Dis.* **1996**, *174*, 1238−1248.
[9] S. Gulati, D. P. McQuillen, R. E. Mandrell, D. B. Jani, P. A. Rice, *J. Infect. Dis.* **1996**, *174*, 1223−1237.
[10] C. Bernlind, S. Oscarson, *J. Org. Chem.* **1998**, *63*, 7780−7788.
[11] R. Yamasaki, H. Koshino, S. Kurono, Y. Nishinaka, D. P. McQuillen, A. Kume, S. Gulati, P. A. Rice, *J. Biol. Chem.* **1999**, *274*, 36550−36558.
[12] R. Yamasaki, D. E. Kerwood, H. Schneider, K. P. Quinn, J. M. Griffiss, R. E. Mandrell, *J. Biol. Chem.* **1994**, *269*, 30345−30351.
[13] R. Yamasaki, A. Takajo, H. Kubo, T. Matsui, K. Ishii, M. Yoshida, *J. Carbohydr. Chem.* **2001**, *20*, 171−180.
[14] K. Ishii, H. Kubo, R. Yamasaki, *Carbohydr. Res.* **2002**, *337*, 11−20.
[15] H. Kubo, K. Ishii, H. Koshino, K. Toubetto, K. Naruchi, R. Yamasaki, *Eur. J. Org. Chem.* **2004**, 1202−1213, preceding paper.
[16] N. J. Phillips, M. A. Apicella, J. M. Griffiss, B. W. Gibson, *Biochemistry* **1993**, *32*, 2003−2012.
[17] S. P. Gaucher, M. T. Cancilla, N. J. Philips, B. W. Gibson, J. A. Leary, *Biochemistry* **2000**, *39*, 12406−12414.
[18] E. Mark, E. Zbiral, H. Brandstetter, *Monatsh. Chem.* **1980**, *111*, 289−307.
[19] T. Halmos, R. Montserret, J. Filippi, K. Antonakis, *Carbohydr. Res.* **1987**, *170*, 57−69.
[20] M. S. Arias Pérez, M. J. Santos, *Tetrahedron* **1996**, *52*, 10785−10798.
[21] M. S. Arias Pérez, M. S. López, M. J. Santos, *J. Chem. Soc., Perkin Trans. 2* **2002**, 1549−1552.
[22] A. R. Vaino, W. A. Szarek, *Chem. Commun.* **1996**, *21*, 2351−2352.
[23] A. B. Smith, G. R. Ott, *J. Am. Chem. Soc.* **1996**, *118*, 13095−13096.
[24] M. J. Robins, V. Samano, M. D. Johnson, *J. Org. Chem.* **1990**, *55*, 410−412.
[25] S. Ogawa, M. Ashiura, C. Uchida, *Carbohydr. Res.* **1998**, *307*, 83−95.
[26] A. Demchenko, T. Stauch, G. J. Boons, *Synlett* **1997**, *7*, 818−820.
[27] A. V. Demchenko, E. Rousson, G. J. Boons, *Tetrahedron Lett.* **1999**, *40*, 6523−6526.
[28] B. Wegmann, R. R. Schmidt, *J. Carbohydr. Chem.* **1987**, *6*, 357−375.
[29] H. Lönn, *J. Carbohydr. Chem.* **1987**, *6*, 301−306.
[30] H. A. Orgueira, A. Bartolozzi, P. Schell, R. Litjens, E. R. Palmacci, P. H. Seeberger, *Chem. Eur. J.* **2003**, *9*, 140−169.
[31] Y. Nakahara, H. Iijima, T. Ogawa, *Carbohydr. Lett.* **1994**, *1*, 99−106.
[32] A. Ishii, H. Hojo, A. Kobayashi, K. Nakamura, Y. Nakahara, Y. Ito, *Tetrahedron* **2000**, *56*, 6235−6243.
[33] J. Tamura, K. W. Neumann, T. Ogawa, *Liebigs Ann.* **1996**, *8*, 1239−1257.
[34] N. C. R. van Straten, N. Kriek, C. M. Timmers, S. C. M. Wigchert, G. A. van der Marel, J. H. van Boom, *J. Carbohydr. Chem.* **1997**, *16*, 947−966.
[35] B. Grzeszczyk, A. Zamojski, *Carbohydr. Res.* **1994**, *262*, 49−57.
[36] P. J. Garegg, S. Oscarson, M. Szönyi, *Carbohydr. Res.* **1990**, *205*, 125−132.
[37] P. J. Garegg, S. Oscarson, H. Ritzén, M. Szönyi, *Carbohydr. Res.* **1992**, *228*, 121−128.
[38] A. D. Cox, J. C. Wright, M. A. J. Gidney, S. Lacelle, J. S. Plested, A. Martin, E. R. Moxon, J. C. Richards, *Eur. J. Biochem.* **2003**, *270*, 1759−1766.
[39] G. O. Aspinall, M. A. Monteiro, H. P. Pang, L. A. Kurjanczyk, J. L. Penner, *Carbohydr. Res.* **1995**, *279*, 227−244.

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